

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
8 April 2004 (08.04.2004)

PCT

(10) International Publication Number
WO 2004/029055 A1

(51) International Patent Classification⁷: **C07D 487/04**,
487/06, 519/00, A61P 29/00

BACON, Kevin [GB/JP]; 5-15-912, Koyo-cho Naka,
Higashinada-ku, Kobe-shi, Hyogo 658-0032 (JP).

(21) International Application Number:
PCT/EP2003/010377

(74) Common Representative: **BAYER HEALTHCARE**
AG; Law and Patents, Patents and Licensing, 51368
Leverkusen (DE).

(22) International Filing Date:
18 September 2003 (18.09.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02021861.6 30 September 2002 (30.09.2002) EP

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Burasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **BAYER**
HEALTHCARE AG [DE/DE]; 51368 Leverkusen (DE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **SHIMADA, Mit-**
suyuki [JP/JP]; 4-7-905, Kyobatejikatahigashigawa-cho,
Nara-shi, Nara 630-8323 (JP). **MURATA, Toshiki** [JP/JP];
1-3-501, Nakano-cho, Ikoma-shi, Nara 630-0267 (JP).
FUCHIKAMI, Kinji [JP/JP]; 7-1-8-A 103, Umemidai,
Kizu-cho, Soraku-gun, Kyoto 619-0215 (JP). **TSU-**
JISHITA, Hideki [JP/JP]; 1-37-2-522, Seikadai,
Seika-cho, Soraku-gun, Kyoto 619-0238 (JP). **OMORI,**
Naoki [JP/JP]; 1-4-8-A 102, Umemidai, Kizu-cho, So-
raku-gun, Kyoto 619-0213 (JP). **KATO, Issei** [JP/JP];
17-2-202, Surugamachi, Nara-shi, Nara 630-8357 (JP).
MIURA, Mami [JP/JP]; 1-1365-3-202, Daiwa-cho,
Gakuen, Nara 631-0041 (JP). **URBAHNS, Klaus** [DE/JP];
6-3-1-301, Kusugaoka-cho, Nada-ku, Kobe-shi, Hyogo
657-0024 (JP). **GANTNER, Florian** [AT/JP]; 1-5-40-302,
Dogashiba, Tennoji-ku, Osaka-shi, Osaka 540-0033 (JP).

Declaration under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii)) for all designations*

Published:

— *with international search report*
— *before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments*

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

WO 2004/029055 A1

(54) Title: **FUSED AZOLE-PYRIMIDINE DERIVATIVES**

(57) Abstract: The present invention relates to novel fused azolepyrimidine derivatives, processes for preparing them and pharmaceutical preparations containing them. The fused azolepyrimidine derivatives of the present invention exhibit enhanced potency for phosphatidylinositol-3-kinase (P13K) inhibition, especially for P13K- γ inhibition and can be used for the prophylaxis and treatment of diseases associated with P13K and particularly with P13K- γ activity. More specifically, the azole derivatives of the present invention are useful for treatment and prophylaxis of diseases as follows: inflammatory and immunoregulatory disorders, such as asthma, atopic dermatitis, rhinitis, allergic diseases, chronic obstructive pulmonary disease (COPD), septic shock, joint diseases, autoimmune pathologies such as rheumatoid arthritis, and Graves' disease, cancer, myocardial contractility disorders, heart failure, thromboembolism, ischemia, and atherosclerosis. The compounds of the present invention are also useful for pulmonary hypertension, renal failure, cardiac hypertrophy, as well as neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, diabetes and focal ischemia, since the diseases also relate to P13K activity in a human or animal subject.

FUSED AZOLE-PYRIMIDINE DERIVATIVES

DETAILED DESCRIPTION OF INVENTION

5

Technical Field

The present invention relates to novel fused azolepyrimidine derivatives, processes for preparing them and pharmaceutical preparations containing them. The fused
10 azolepyrimidine derivatives of the present invention exhibit enhanced potency for phosphatidylinositol-3-kinase (PI3K) inhibition, especially for PI3K- γ inhibition and can be used for the prophylaxis and treatment of diseases associated with PI3K and particularly with PI3K- γ activity.

15 More specifically, the fused azolepyrimidine derivatives of the present invention are useful for treatment and prophylaxis of diseases as follows: inflammatory and immunoregulatory disorders, such as asthma, atopic dermatitis, rhinitis, allergic diseases, chronic obstructive pulmonary disease (COPD), septic shock, joint diseases, autoimmune pathologies such as rheumatoid arthritis, and Graves' disease,
20 cancer, myocardial contractility disorders, heart failure, thromboembolism, ischemia, and atherosclerosis.

The compounds of the present invention are also useful for pulmonary hypertension, renal failure, cardiac hypertrophy, as well as neurodegenerative disorders such as
25 Parkinson's disease, Alzheimer's disease, diabetes and focal ischemia, since the diseases also relate to PI3K activity in a human or animal subject.

BACKGROUND ART

30 Signal transduction pathways originating from chemoattractant receptors are considered to be important targets in controlling leukocyte motility in inflammatory

- 2 -

diseases. Leukocyte trafficking is controlled by chemoattractant factors that activate heterotrimeric G-protein coupled receptors (GPCRs) and thereby trigger a complex variety of downstream intracellular events. Signal transduction at one of the pathways, that results in mobilization of intracellular free Ca^{2+} , cytoskeletal reorganisation, and directional movement depends on lipid-derived second messengers produced by phosphoinositide 3-kinase (PI3K) activity [1,2].

PI3K phosphorylates the D3-hydroxyl position of the membrane phospholipid phosphatidylinositol-4,5-bisphosphate ($\text{PtdIns}(4,5)\text{P}_2$) to yield phosphatidylinositol-3,4,5-trisphosphate ($\text{PtdIns}(3,4,5)\text{P}_3$). Based on substrate specificity and protein structure, the PI3K family comprises three classes [4-6]. Of particular interest in leukocyte migration are class I PI3Ks, which are all involved in receptor-induced inflammatory cellular responses and are further divided into the subclasses IA (p110 α , β , δ) and IB (p110 γ).

Class IA enzymes (p110 α , β , δ) associate with a p85 adapter subunit, which contains two SH2 domains, to form a heterodimeric complex. This complex is able to recognize phosphotyrosine YxxM motifs, resulting in association with receptor tyrosine kinases and subsequent activation of the enzyme through receptor tyrosine kinases [1, 2]. The class IA subtypes are considered to be associated with cell proliferation and carcinogenesis. The IA subtypes bind to activated ras oncogene, which is found in many cancers, to express their enzyme activity. It has also found that both p110 α and β play important roles in human cancer growth [3].

Class IB (p110 γ) enzyme, whose expression is largely confined to leukocytes, is activated by the G protein $\beta\gamma$ complex, and functions downstream of seven transmembrane chemoattractant receptors [7-9]. The p101 adapter protein, which bears no resemblance to any other known protein, is essential for the G protein $\beta\gamma$ responsiveness of the p110 γ (PI3K γ). [10-12].

- 3 -

Recent studies in mice lacking functional PI3K γ (PI3K γ ^{-/-} mice), which were viable, fertile, and displayed a normal life span in a conventional mouse facility, have revealed that neutrophils are unable to produce PtdIns(3,4,5) P_3 when stimulated with GPCR agonists such as fMLP, C5a or IL-8. This demonstrates that PI3K γ is the sole
5 PI3K that is coupled to these GPCRs in these cells [13-16]. Moreover, PtdIns(3,4,5) P_3 -dependent activation of protein kinase B (PKB) was also absent in those neutrophils, while PKB could still be activated by GM-CSF or IgG/C3b-coated zymosan via either p110 α , β or δ . At the same time, G-protein-mediated responses such as PLC β activation were intact. PI3K γ ^{-/-} mice showed impaired thymocyte
10 development and increases in neutrophil, monocyte, and eosinophil populations [14]. Furthermore, neutrophils and macrophages isolated from PI3K γ ^{-/-} mice exhibited severe defects in migration and respiratory burst in response to GPCR agonists and chemotactic agents [14,16]. Expression of PI3K γ was also examined in transgenic mice expressing green fluorescence protein (GFP) under the control of the
15 endogenous PI3K γ promoter. GFP was detected in spleen and bone marrow cells, and neutrophils, suggesting that the expression of PI3K γ is restricted to hematopoietic cells [15]. Collectively, the class IB phosphoinositide 3-kinase PI3K γ seems to be pivotal in the control of leukocyte trafficking and accordingly the development of isotype-selective inhibitors of PI3K γ should be an attractive anti-inflammatory
20 strategy.

Hypertrophic responses can be initiated by PI3K signaling pathways. Currently new research was published which identify a function for PTEN- PI3K γ pathway in the modulation of heart muscle contractility. Whereas PI3K α mediates the alteration in
25 cell size seen during heart hypertrophy up to heart failure, PI3K γ acts as a negative regulator of cardiac contractility.

PTEN is a dual-specificity protein phosphatase recently implicated as a phospho-
inositide phosphatase in cellular growth signaling. The tumor suppressor PTEN is
30 shown to dephosphorylate phosphatidylinositol 3,4,5-triphosphate (PIP3) which is an important second messenger generated specifically by the actions of PI3K. The

- 4 -

PTEN reduces the levels of PIP3 within the cells and antagonizes PI3K mediated cellular signaling. It is also reported that expression of dominant-negative PTEN in rat cardiomyocytes in tissue culture results in hypertrophy.

5 PI3K γ modulates baseline cAMP levels and controls contractility in cells. This study also indicates that alterations in baseline cAMP level contribute to the increased contractility in mutant mice [17].

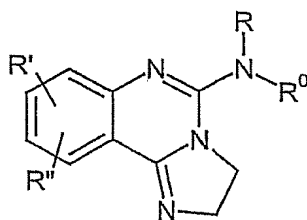
10 Therefore, this research result shows that PI3K γ is involved in myocardial contractility and therefore the inhibitors would be potential treatments of congestive heart failure, ischemia, pulmonary hypertension, renal failure, cardiac hypertrophy, atherosclerosis, thromboembolism, and diabetes.

15 A inhibitor of PI3K, which is expected to block signaltransduction from GPCR and the activation of various immune cells, should have a broad anti-inflammatory profile with potential for the treatment of inflammatory and immunoregulatory disorders, [2] including asthma, atopic dermatitis, rhinitis, allergic diseases, chronic obstructive pulmonary disease (COPD), septic shock, joint diseases, autoimmune pathologies such as rheumatoid arthritis, and Graves' disease, diabetes, cancer, myocardial
20 contractility disorders, thromboembolism [18], and atherosclerosis.

Some PI3-kinase inhibitors has been identified: wortmannin, originally isolated as a fungal toxin from *Penicillium wortmannii* [19], the closely related but less well characterized demethoxyviridin and LY294002, a morpholino derivative of the
25 broad-spectrum kinase inhibitor quercetin [20].

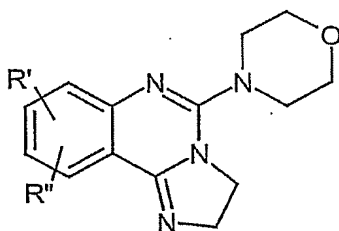
US 3644354 discloses 5-substituted 2,3, dihydroimidazo[1,2-c]quinazolines represented by the general formula:

- 5 -



wherein R and R⁰ is independently, hydrogen, lower alkyl, lower alkenyl; R' and R'' are independently, hydrogen, halogen, lower alkyl, lower alkoxy

5 or



as a hypotensive agents and coronary dilators

10 However, none of the references discloses fused azolepyrimidine such as, but not limited to, azole-quinazoline, azole-pyridopyrimidine, azole-pyrimidopyrimidine, azole-pyrimidopyridazine, azole-pyrimidotriazine, azole-pteridine, azole-pyrimido-tetrazine and other derivatives having acylated amine or -CR⁵R⁶-C(O)- (R⁵ is hydrogen or C₁₋₆ alkyl and R⁶ is halogen, hydrogen, or C₁₋₆ alkyl) linker at the 5- or 6 position of the fused azolepyrimidine also having PI3K inhibitory activity.

15

The development of a compound which is useful for treatment and prophylaxis of inflammatory, cancer and/or myocardial contractility disorders associated with PI3K activity has been still desired.

20

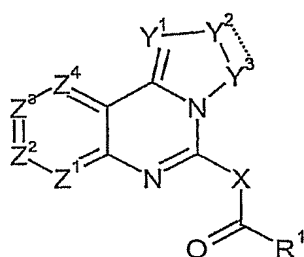
Summary of the invention

As a result of extensive studies on chemical modification of the fused azolepyrimidine derivatives, the present inventors have found that the compounds of novel

- 6 -

chemical structure related to the present invention have PI3K inhibitory activity and particularly have PI3K- γ inhibitory activity. The present invention has been accomplished based on these findings.

- 5 This invention is to provide novel fused azolepyrimidine derivatives of the formula (I) their tautomeric and stereoisomeric forms, and salts thereof.



wherein

10

X represents CR⁵R⁶ or NH;

Y¹ represents CR³ or N;

15

Chemical bond between Y²—Y³ represents a single bond or double bond,

with the proviso that when the Y²—Y³ represents a double bond,

Y² and Y³ independently represent CR⁴ or N, and

20

when Y²—Y³ represents a single bond, Y² and Y³ independently represent CR³R⁴ or NR⁴;

Z¹, Z², Z³ and Z⁴ independently represent CH, CR² or N;

25

- 7 -

- R¹ represents aryl optionally having 1 to 3 substituents selected from R¹¹, C₃₋₈ cycloalkyl optionally having 1 to 3 substituents selected from R¹¹, C₁₋₆ alkyl optionally substituted by aryl, heteroaryl, C₁₋₆ alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,
- C₁₋₆ alkoxy optionally substituted by carboxy, aryl, heteroaryl, C₁₋₆ alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,
- or
- a 3 to 15 membered mono- or bi-cyclic heterocyclic ring that is saturated or unsaturated, and contains 1 to 3 heteroatoms selected from the group consisting of N, O and S, and optionally having 1 to 3 substituents selected from R¹¹
- wherein
- R¹¹ represents
- halogen, nitro, hydroxy, cyano, carboxy, amino, N-(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, N-(formyl)-N-(C₁₋₆alkyl)amino, N-(C₁₋₆alkanesulfonyl) amino, N-(carboxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, N-(C₁₋₆alkoxycarbonyl)amino, N-[N,N-di(C₁₋₆alkyl)amino methylene]amino, N-[N,N-di(C₁₋₆alkyl)amino (C₁₋₆ alkyl)methylene]amino, N-[N,N-di(C₁₋₆alkyl)amino C₂₋₆alkenyl]amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl, C₃₋₈cycloalkyl, C₁₋₆ alkylthio, C₁₋₆alkanesulfonyl, sulfamoyl, C₁₋₆alkoxycarbonyl, N-arylamino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R¹⁰¹, N-(aryl C₁₋₆alkyl)amino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R¹⁰¹, aryl C₁₋₆alkoxy-carbonyl wherein said aryl moiety is optionally having 1 to 3 substituents selected from R¹⁰¹,
- C₁₋₆alkyl optionally substituted by
- mono-, di- or tri- halogen, amino, N-(C₁₋₆alkyl)amino or N,N-di(C₁₋₆alkyl)amino,

- 8 -

- C₁₋₆alkoxy optionally substituted by
 mono-, di- or tri- halogen, N-(C₁₋₆alkyl)sulfonamide, or N-(aryl)sulfonamide,
 or
 a 5 to 7 membered saturated or unsaturated ring having 1 to 3 heteroatoms
 5 selected from the group consisting of O, S and N, and optionally having 1 to
 3 substituents selected from R¹⁰¹
 wherein
 R¹⁰¹ represents
 halogen, carboxy, amino, N-(C₁₋₆ alkyl)amino, N,N-di(C₁₋₆alkyl)amino,
 10 aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)amino-
 carbonyl, pyridyl,
 C₁₋₆ alkyl optionally substituted by cyano or mono- di- or tri- halogen,
 or
 C₁₋₆alkoxy optionally substituted by cyano, carboxy, amino, N-(C₁₋₆
 15 alkyl)amino, N,N-di(C₁₋₆alkyl)amino, aminocarbonyl, N-(C₁₋₆alkyl)amino-
 carbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl or mono-, di- or tri- halogen;
- R² represents hydroxy, halogen, nitro, cyano, amino, N-(C₁₋₆alkyl)amino, N,N-
 di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)-N-
 20 (C₁₋₆alkyl)amino, C₁₋₆ acyloxy, aminoC₁₋₆ acyloxy, C₂₋₆alkenyl, aryl,
 a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3
 heteroatoms selected from the group consisting O, S and N, and optionally
 substituted by
 hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, amino C₁₋₆alkyl, N-
 25 (C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, N-
 (C₁₋₆alkyl)carbonylamino, phenyl, phenyl C₁₋₆ alkyl, carboxy,
 C₁₋₆alkoxycarbonyl, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-
 di(C₁₋₆alkyl)amino,
 -C(O)- R²⁰
 30 wherein

- 9 -

R²⁰ represents C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, or a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by

5 C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, phenyl, or benzyl,

C₁₋₆ alkyl optionally substituted by R²¹

or

10 C₁₋₆ alkoxy optionally substituted by R²¹

wherein

R²¹ represents cyano, mono-, di or tri- halogen, hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N- (hydroxyC₁₋₆ alkyl) amino, N- (halophenylC₁₋₆ alkyl) amino, amino C₂₋₆ alkylenyl, C₁₋₆ alkoxy,

15 hydroxyC₁₋₆ alkoxy, -C(O)- R²⁰¹, -NHC(O)- R²⁰¹, C₃₋₈cycloalkyl, isoindolino, phthalimidyl, 2-oxo-1,3-oxazolidinyl, aryl or a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N optionally substituted by

20 hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxycarbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, aminoC₁₋₆alkyl, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, or benzyl,

wherein

25 R²⁰¹ represents hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N- (halophenylC₁₋₆ alkyl) amino, C₁₋₆alkyl, aminoC₁₋₆ alkyl, aminoC₂₋₆ alkylenyl, C₁₋₆ alkoxy, a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N optionally substituted by

- 10 -

hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino or benzyl;

5 R³ represents hydrogen, halogen, aminocarbonyl, or C₁₋₆ alkyl optionally substituted by aryl C₁₋₆ alkoxy or mono-, di- or tri- halogen;

 R⁴ represents hydrogen or C₁₋₆ alkyl;

10 R⁵ represents hydrogen or C₁₋₆ alkyl; and

 R⁶ represents halogen, hydrogen or C₁₋₆ alkyl.

15 The compounds of the present invention show PI3K inhibitory activity and PI3K- γ inhibitory activity. They are, therefore, suitable for the production of medicament or medical composition, which may be useful for treatment and prophylaxis of PI3K and/or PI3K- γ related diseases for example, inflammatory and immunoregulatory disorders, such as asthma, atopic dermatitis, rhinitis, allergic diseases, chronic obstructive pulmonary disease (COPD), septic shock, joint diseases, autoimmune

20 pathologies such as rheumatoid arthritis, and Graves' disease, myocardial contractility disorders, heart failure, thromboembolism, ischemia, cardiac hypertrophy, atherosclerosis and cancer such as skin cancer, bladder cancer, breast cancer, uterus cancer, ovary cancer, prostate cancer, lung cancer, colon cancer, pancreas cancer, renal cancer, gastric cancer, brain tumor, leukemia, etc.

25

 The compounds of the present invention are also useful for treatment of pulmonary hypertension, renal failure, Huntington's chorea and cardiac hypertrophy, as well as neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, diabetes and focal ischemia, since the diseases also relate to PI3K activity in a

30 human or animal subject.

- 11 -

This invention is also to provide a method for treating or preventing a disorder or disease associated with PI3K activity, especially with PI3K- γ activity, in a human or animal subject, comprising administering to said subject a therapeutically effective amount of the fused azolepyrimidine derivatives shown in the formula (I), its
5 tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof.

Further this invention is to provide a use of the fused azolepyrimidine derivatives shown in the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof in the preparation of a medicament.

10

In one embodiment, the present invention provides the fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof ; wherein

15 X represents CR^5R^6 or NH;

Y^1 represents CR^3 or N;

Chemical bond between $Y^2=Y^3$ represents a single bond or double bond,
20 with the proviso that when the $Y^2=Y^3$ represents a double bond,
 Y^2 and Y^3 independently represent CR^4 or N, and
when $Y^2=Y^3$ represents a single bond, Y^2 and Y^3 independently represent CR^3R^4 or NR^4 ;

25 Z^1, Z^2, Z^3 and Z^4 independently represent CH, CR^2 or N;

R^1 represents

C_{1-6} alkyl optionally substituted by

mono-, di- or tri- halogen, phenyl, methoxyphenyl, phenoxy, or thienyl,

30 C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, phenyl, methoxy-phenyl, phenoxy, or thienyl,

- 12 -

or

one of the following carbocyclic and heterocyclic rings selected from the group consisting of cyclopropyl, cyclohexyl, piperidinyl, piperazinyl, pyrrolyl, pyrazolyl, furyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, isoimidazolyl, pyrazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1-benzothiophenyl, benzothiazolyl, benzimidazolyl, 3H-imidazo[4,5-b]pyridinyl, benzotriazolyl, indolyl, indazolyl, imidazo[1,2-a]pyridinyl, quinoliny, and 1,8-naphthyridinyl,

wherein

said carbocyclic and heterocyclic rings optionally substituted with 1 to 3 substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, carboxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, N-(C₁₋₆alkoxycarbonyl)amino, N-(formyl)-N-(C₁₋₆alkyl)amino, N[N,N-di(C₁₋₆alkyl)amino methylene]amino, N[N,N-di(C₁₋₆alkyl)amino (C₁₋₆alkylene)methylene]amino, N[N,N-di(C₁₋₆alkyl)amino C₂₋₆alkenyl]amino, C₁₋₆ alkylthio, C₁₋₆alkanesulfonyl, sulfamoyl, C₁₋₆alkoxy, C₁₋₆alkoxycarbonyl, pyrrolyl, imidazolyl, pyrazolyl, pyrrolidinyl, pyridyl, phenyl C₁₋₆alkoxycarbonyl,

thiazolyl optionally substituted by

pyridyl,

piperazinyl optionally substituted by C₁₋₆ alkyl or C₁₋₆alkoxy

and

C₁₋₆alkyl optionally substituted by mono-, di- or tri- halogen;

R² represents hydroxy, halogen, nitro, cyano, carboxy, amino, N-(C₁₋₆alkyl)amino, N-(hydroxy C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxy C₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, C₂₋₆alkenyl, C₁₋₆alkoxycarbonyl, amino-carbonyl, C₁₋₆acyloxy, aminoC₁₋₆ acyloxy, furyl, morpholino, phenyl, piperidino, aryl,

- 13 -

pyrrolidinyl optionally substituted by C₁₋₆acylamino,
piperidino optionally substituted by hydroxy, C₁₋₆ alkyl, carboxy, aminocarbonyl, N-
(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)aminocarbonyl,

5

piperazinyl optionally substituted by C₁₋₆ alkyl,

C₁₋₆ alkyl optionally substituted by cyano, mono-, di- or tri- halogen, hydroxy,
amino, N-(C₁₋₆alkyl)amino, N-(hydroxy C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino,
10 C₃₋₆ cycloalkyl, tetrazolyl, tetrahydropyranyl, morpholino, phthalimidyl, 2-oxo-
1,3oxazolidinyl, phenyl,
-C(O)- R²⁰¹,

pyrrolidinyl optionally substituted by C₁₋₆acylamino,
15 piperidino optionally substituted by hydroxy, C₁₋₆ alkyl, carboxy, aminocarbonyl, N-
(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)aminocarbonyl,

or

piperazinyl optionally substituted by C₁₋₆ alkyl,

20

wherein

R²⁰¹ represents hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-
(halobenzyl)amino, C₁₋₆alkyl, C₁₋₆ alkoxy, tetrazolyl, tetrahydropyranyl, morpholino,
25 pyrrolidinyl optionally substituted by C₁₋₆acylamino,
piperidino optionally substituted by hydroxy, C₁₋₆ alkyl, carboxy, aminocarbonyl, N-
(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)aminocarbonyl,

or

piperazinyl optionally substituted by C₁₋₆ alkyl,

30

C₁₋₆ alkoxy optionally substituted by cyano, mono-, di- or tri- halogen, hydroxy,
C₁₋₆alkoxy, hydroxy C₁₋₆ alkoxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alk-

- 14 -

yl)amino, pyrrolyl, tetrazolyl, tetrahydropyranyl, morpholino, phthalimidyl, 2-oxo-1,3-oxazolidinyl, phenyl, -C(O)-R²⁰¹,

pyrrolidinyl optionally substituted by C₁₋₆acylamino,

5 piperidino optionally substituted by hydroxy, C₁₋₆ alkyl, carboxy, aminocarbonyl, N-(C₁₋₆-alkyl)aminocarbonyl, or N,N-di(C₁₋₆-alkyl)aminocarbonyl,

or

piperazinyl optionally substituted by C₁₋₆ alkyl,

wherein

10

R²⁰¹ represents hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N(halobenzyl)amino, C₁₋₆ alkyl, C₁₋₆ alkoxy, amino C₂₋₆ alkylenyl, tetrazolyl, tetrahydropyranyl, morpholino,

15

pyrrolidinyl optionally substituted by C₁₋₆acylamino,

piperidino optionally substituted by hydroxy, C₁₋₆ alkyl, carboxy, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)aminocarbonyl,

20

or

piperazinyl optionally substituted by C₁₋₆alkyl;

R³ represents hydrogen, halogen, C₁₋₆ alkyl optionally substituted by aminocarbonyl, arylC₁₋₆ alkoxy, or mono-, di- or tri-halogen;

25

R⁴ represents hydrogen or C₁₋₆ alkyl;

R⁵ represents hydrogen or C₁₋₆ alkyl; and

30

R⁶ represents hydrogen, halogen or C₁₋₆ alkyl.

- 15 -

In another embodiment, the present invention provides the fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof: wherein

X represents CR^5R^6 or NH ;

5

Y^1 represents N ;

Y^2 and Y^3 represent CR^3R^4 ;

10 Chemical bond between $Y^2=Y^3$ represents a single bond

Z^4 represents CH ;

Z^1 , Z^2 and Z^3 independently represent N , CH or CR^2 ;

15

R^1 represents cyclopropyl, cyclopentyl, cyclohexyl, 2-furyl, 3-furyl, imidazolyl, pyrimidinyl, pyridazinyl, piperazinyl, 1,2,3-thiadiazolyl, 1,3-benzothiazolyl, quinolyl, 3H-imidazo[4,5-b]pyridinyl, 1H-pyrrol-2-yl optionally substituted by C_{1-6} alkyl,

20 1H-pyrrol-3-yl optionally substituted by C_{1-6} alkyl, pyrazolyl optionally substituted by 1 or 2 C_{1-6} alkyl, isoxazolyl optionally substituted by 1 or 2 C_{1-6} alkyl,

2-thienyl optionally substituted by chloro, nitro, cyano, or C_{1-6} alkyl,

3-thienyl optionally substituted by chloro, nitro, cyano, or C_{1-6} alkyl,

25 piperidinyl optionally substituted by C_{1-6} alkoxycarbonyl, or benzyloxy-carbonyl,

phenyl optionally substituted by 1 to 3 substituents selected from the group consisting of fluoro, chloro, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, amino, N -(C_{1-6} alkyl)amino, N -(C_{1-6} acyl)amino,

30 N -(C_{1-6} alkoxycabonyl)amino, N,N -di(C_{1-6} alkyl)amino, N -(formyl)- N - C_{1-6}

- 16 -

alkyl amino, C₁₋₆ alkylthio, C₁₋₆alkanesulfonyl, sulfamoyl, pyrrolyl, imidazolyl, pyrazolyl, and piperazinyl optionally substituted by C₁₋₆alkyl,

5 pyridyl optionally substituted by 1 or 2 substituents selected from the group consisting of chloro, hydroxy, carboxy, C₁₋₆alkoxy, C₁₋₆alkylthio, amino, N-(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, N-(C₁₋₆alkane)sulfonyl amino, N[N,N-di(C₁₋₆alkyl)amino methylene]amino, and C₁₋₆alkyl optionally substituted by tri halogen,

10 pyrazinyl optionally substituted by C₁₋₆alkyl,

1,3-thiazolyl optionally substituted by 1 or 2 substituents selected from the group consisting of C₁₋₆alkyl, pyridyl and N-(C₁₋₆alkoxycarbonyl)amino, indolyl optionally substituted by C₁₋₆alkyl,

15 benzimidazolyl optionally substituted by C₁₋₆alkyl or tri-halo C₁₋₆alkyl, 1,2,3-benzotriazolyl optionally substituted by C₁₋₆alkyl, 1,8-naphthyridinyl optionally substituted by

C₁₋₆alkyl optionally substituted by tri halogen, C₁₋₆ alkyl optionally substituted by tri-halogen, phenyl, phenoxy, or thienyl, or

20 C₁₋₆alkoxy optionally substituted by phenyl, phenoxy, or thienyl;

R² represents fluoro, chloro, bromo, hydroxy, nitro, vinyl, cyano, amino, aminoacetoxy, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, 2-furyl, piperidino, morpholino, phenyl,

pyrrolidinyl optionally substituted by acetamido, piperidino optionally substituted by hydroxy, piperazinyl optionally substituted by methyl, benzyl, C₁₋₆alkoxy-carbonyl, or aminocarbonyl,

30

- 17 -

C₁₋₆ alkyl optionally substituted by cyano, tri-fluoro, carboxy, methoxycarbonyl, aminocarbonyl, tert-butoxycarbonyl, tetrahydropyranyl, or morpholino,

5 C₁₋₆ alkoxy optionally substituted by hydroxy, cyano, methoxy, methoxycarbonyl, tert-butoxycarbonyl, carboxy, aminoacetyl, dimethylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, isopropylaminocarbonyl, fluoro-benzylaminocarbonyl, cyclopropyl, pyrrolidinyl, piperidino, tetrahydropyranyl, morpholino, morpholinocarbonyl, 2-oxo-10 1,3-oxazolidin-4-yl, phthalimid-N-yl, or hydroxy C₁₋₆ alkyleneoxy,

R³ represents hydrogen;

15 R⁴ represents hydrogen;

R⁵ represents hydrogen; and

R⁶ represents hydrogen.

20

In another embodiment, the present invention provides the fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

X represents CR⁵R⁶ or NH;

25 Y¹ represents N;

Y² and Y³ represent CR³R⁴;

Chemical bond between Y²—Y³ represents a single bond

30

Z³ and Z⁴ represent CH;

- 18 -

Z^1 and Z^2 independently represent CH or CR^2 ;

5 R^1 represents 3H-imidazo[4,5-b]pyridinyl, benzimidazolyl pyridyl optionally substituted by hydroxy, amino, acetamido, methoxybenzyloxy or methylsulfonylamino,

or

10 1,3-thiazolyl optionally substituted by 1 or 2 methyl;

R^2 represents fluoro, chloro, bromo, morpholino, piperazinyl, methylpiperazinyl, methyl, tri-fluoro methyl, or

15 C_{1-6} alkoxy optionally substituted by hydroxy, cyano, carboxy, dimethylaminocarbonyl, tetrahydropyranyl, morpholino, morpholinocarbonyl, tetrazolyl, or phthalimid-N-yl;

R^3 represents hydrogen;

20 R^4 represents hydrogen;

R^5 represents hydrogen; and

25 R^6 represents hydrogen.

In another embodiment, the present invention provides the fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

30

X represents CR^5R^6 or NH;

- 19 -

Y^1 represents N;

Y^2 and Y^3 represent CR^3R^4 ;

5

Chemical bond between $Y^2=Y^3$ represents a single bond.

Z^3 and Z^4 represent CH;

10 Z^1 and Z^2 independently represent CH or CR^2 ;

In another embodiment, the present invention provides the fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

15 X represents CR^5R^6 or NH;

Y^1 represents N;

Y^2 and Y^3 represent CR^3R^4 ;

20

Chemical bond between $Y^2=Y^3$ represents a single bond

Z^1 and Z^4 represent CH;

25 Z^2 and Z^3 independently represent CH or CR^2 ;

In another embodiment, the present invention provides the fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

30 X represents CR^5R^6 or NH;

- 20 -

Y^1 represents N;

Y^2 and Y^3 represent CR^3R^4 ;

5 Chemical bond between $Y^2 \text{---} Y^3$ represents a single bond;

Z^1 , Z^3 and Z^4 represent CH;

Z^2 represents CR^2 ;

10

The preferable compounds of the present invention are as follows:

N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
2-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-pyridin-3-yl-
ethylenol;

15 N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-
carboxamide;

6-(acetamido)-N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotin-
amide;

20 N-{5-[2-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxy-
vinyl]pyridin-2-yl}acetamide;

2-({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-
c]quinazolin-8-yl} oxy)-N,N-dimethylacetamide;

2-[7-methoxy-8-(tetrahydro-2H-pyran-2-ylmethoxy)-2,3-dihydroimidazo[1,2-
c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;

25 2-[8-(2-hydroxyethoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-
pyridin-3-ylethylenol;

({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-
c]quinazolin-8-yl} oxy)acetic acid;

30 4-({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-
c]quinazolin-8-yl} oxy)butanoic acid;

- 21 -

- ({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)acetonitrile;
2-[7-methoxy-8-(2H-tetrazol-5-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;
5 2-[7-methoxy-8-(4-morpholin-4-yl-4-oxobutoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;
5-[1-hydroxy-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)vinyl]pyridin-3-ol ;
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;
10 6-(acetamido)-N-(7,9-dimethoxy-8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;
5-hydroxy-N-(7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
15 N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-[(4-methoxybenzyl)oxy]nicotinamide;
N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;
5-hydroxy-N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
20 N-{8-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-(7-bromo-8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
6-amino-N-(8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
25 1-(1H-benzimidazol-5-yl)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)ethylenol;
2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2,4-dimethyl-1,3-thiazol-5-yl)ethylenol;
N-(9-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
30 N-(8-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

- N-(8-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
- N-(8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
- 5 N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
- N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1H-benzimidazole-5-carboxamide;
- N-(7-fluoro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
- 10 N-(7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
- 6-(acetamido)-N-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 15 1-(1H-benzimidazol-5-yl)-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)ethylenol;
- N-{5-[1-hydroxy-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)vinyl]pyridin-2-yl}acetamide;
- 20 6-methyl-N-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 1-(1H-benzimidazol-5-yl)-2-[8-(4-methylpiperazin-1-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]ethylenol;
- N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 25 N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- N-[7-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1H-benzimidazole-5-carboxamide;
- 30 N-(7,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

- 23 -

N-{5-[2-(7,9-dimethoxy-8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide;

N-{5-[2-(7-bromo-9-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide; and

5 2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-pyridin-3-ylethanol;

and its tautomeric or stereoisomeric form, pharmaceutically acceptable salts thereof.

Further, the present invention provides a medicament, which includes one of the
10 compounds, described above and optionally pharmaceutically acceptable excipients.

Alkyl per se and "alk" and "alkyl" in alkane, alkoxy, alkanoyl, alkylamino, alkyl-aminocarbonyl, alkylaminosulphonyl, alkylsulphonylamino, alkoxy-carbonylamino and alkanoylamino represent a linear or branched alkyl radical having
15 generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, sec-butyl, pentyl, n-hexyl, and the like.

Alkylene represents the divalent linear or branched saturated hydrocarbon radical,
20 consisting solely of carbon and hydrogen atoms, having generally 1 to 6 carbon preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methylene, ethylene, 2-methyl-propylene, butylene, 2-ethylbutylene and the like.

25 Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxo, n-hexoxy and the like.

Alkylamino represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino,
30 ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-

- 24 -

methyl-N-n-propylamino, N-isopropyl-N-n-propylamino, N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino, N-n-hexyl-N-methylamino and the like.

Alkylaminocarbonyl represents an radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylamino-carbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-diethylaminocarbonyl, N-ethyl-N-methylaminocarbonyl, N-methyl-N-n-propylaminocarbonyl, N-isopropyl-N-n-propylaminocarbonyl, N-t-butyl-N-methylaminocarbonyl, N-ethyl-N-n-pentylamino-carbonyl, N-n-hexyl-N-methylaminocarbonyl and the like.

Alkylaminosulphonyl represents an alkylaminosulphonyl radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylaminosulphonyl, ethylaminosulphonyl, n-propylaminosulphonyl, isopropylaminosulphonyl, tert-butylaminosulphonyl, n-pentylaminosulphonyl, n-hexylaminosulphonyl, N,N-dimethylaminosulphonyl, N,N-diethylaminosulphonyl, N-ethyl-N-methylamino-sulphonyl, N-methyl-N-n-propylaminosulphonyl, N-isopropyl-N-n-propylaminosulphonyl, N-t-butyl-N-methylaminosulphonyl, N-ethyl-N-n-pentylaminosulphonyl, N-n-hexyl-N-methylaminosulphonyl and the like.

Alkylsulphonyl illustratively and preferably represents methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, tert-butylsulphonyl, n-pentylsulphonyl, n-hexylsulphonyl and the like.

Alkoxy carbonyl illustratively and preferably represents methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl, n-hexoxycarbonyl and the like.

Alkoxy carbonylamino illustratively and preferably represents methoxycarbonylamino, ethoxycarbonylamino, n-propoxycarbonylamino, isopropoxycarbonylamino,

- 25 -

tert-butoxycarbonylamino, n-pentoxycarbonylamino, n-hexoxycarbonylamino and the like.

5 Alkanoylamino illustratively and preferably represents acetamido, ethylcarbonylamino and the like.

Cycloalkyl per se and in cycloalkylamino and in cycloalkylcarbonyl represents a cycloalkyl group having generally 3 to 8 and preferably 5 to 7 carbon atoms, illustratively and preferably representing cyclopropyl, cyclobutyl, cyclopentyl, 10 cyclohexyl, cycloheptyl and the like.

Aryl per se and "aryl" in arylamino, arylcarbonyl, alkoxyaryl, represents a mono- to tricyclic aromatic carbocyclic radical having generally 6 to 14 carbon atoms, illustratively and preferably representing phenyl, naphthyl, phenanthrenyl and the 15 like.

Arylamino represents an arylamino radical having one or two (independently selected) aryl substituents, illustratively and preferably representing phenylamino, diphenylamino, naphthylamino and the like.

20 Heteroaryl per se and "heteroaryl" in heteroarylamino and heteroarylcarbonyl represents an aromatic mono- or bicyclic radical having generally 5 to 15 and preferably 5 or 6 ring atoms and up to 5 and preferably up to 4 hetero atoms selected from the group consisting of S, O and N, illustratively and preferably representing thienyl, 25 furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, thiazolyl, pyrazinyl, pyridinyl, pyrimidinyl, pyridazinyl, thiophenyl, indolyl, isoindolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl, 1,3 benzodioxole, benzofuranyl, benzofuran-2,5-diyl, benzofuran-3,5-diyl, and the like.

30 Heterocyclic per se and heterocyclic ring per se represent a mono- or polycyclic, preferably mono- or bicyclic, nonaromatic heterocyclic radical having generally 4 to

- 26 -

10 and preferably 5 to 8 ring atoms and up to 3 and preferably up to 2 hetero atoms and/or hetero groups selected from the group consisting of N, O, S, SO and SO₂. The heterocyclyl radicals can be saturated or partially unsaturated. Preference is given to 5- to 8-membered monocyclic saturated heterocyclyl radicals having up to two hetero
5 atoms selected from the group consisting of O, N and S, such as illustratively and preferably tetrahydrofuran-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, piperidinyl, morpholino, perhydroazepinyl.

Heterocyclylcarbonyl illustratively and preferably represents tetrahydrofuran-2-
10 carbonyl, pyrrolidine-2-carbonyl, pyrrolidine-3-carbonyl, pyrrolinecarbonyl, piperidinecarbonyl, morpholinecarbonyl, perhydroazepinecarbonyl.

Halogen and H_{alo} represents fluoro, chloro, bromo and/or iodo.

15 Further, the present invention provides a medicament which include one of the compounds described above and optionally pharmaceutically acceptable excipients.

EMBODIMENT OF INVENTION

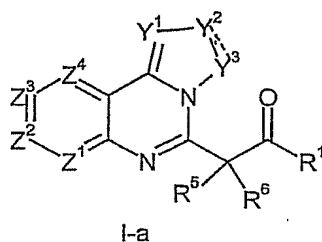
20 The compound of the formula (I) of the present invention can be, but not limited to be, prepared by reactions described below. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting
25 groups are described in "Protective Groups in Organic Synthesis (3rd Edition)" by Greene and Wuts.

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by the Method [A], and [B] below.

30

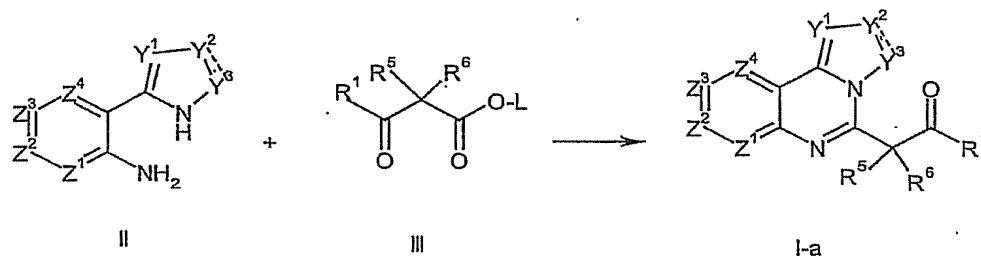
The compound of the formula (I-a):

- 27 -



5 (wherein R^1 , R^5 , R^6 , Y^1 , Y^2 , Y^3 , Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above) can be, but not limited to be, prepared by the following Method A.

Method [A]



10 The compound of formula (I-a) can be prepared, for example, by the reaction of the compound of formula (II) (wherein Y^1 , Y^2 , Y^3 , Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above) with a compound of formula (III) (wherein R^1 , R^5 and R^6 are the same as defined above, and L represents C_{1-6} alkyl).

15 The reaction may be carried out without solvent, or in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO);
20 alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol; water, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

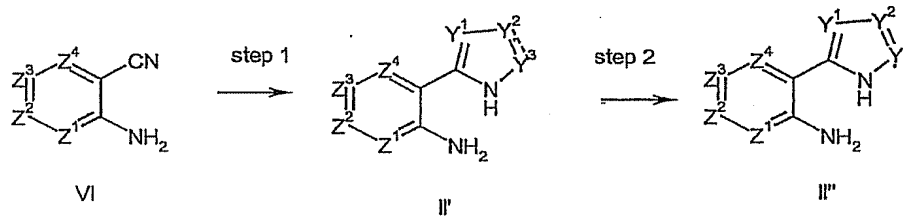
- 28 -

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 10°C to 200°C and preferably about 50°C to 160°C. The reaction may be conducted for, usually, 10 minutes to 48 hours and preferably 30 minutes to 24 hours.

Preparation of the intermediates

The compound of formula (II') (wherein Y^1 , Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above, Y^2 and Y^3 independently represent CR^3R^4 or NR^4 and are connected by single bond) and the compound of formula (II'') (wherein Y^1 , Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above, Y^2 and Y^3 independently represent CH or N and are connected by double bond) can be, but not limited to be, prepared by the following Method [A-i].

Method [A-i]



15

In the step 1, the compound of formula (II') (wherein Y^1 , Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above, Y^2 and Y^3 independently represent CR^3R^4 or NR^4 and are connected by single bond) can be prepared, for example, by the reaction of the compound of formula (VI) (wherein Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above) with an diaminoalkane derivatives such as ethylenediamine.

20

The reaction can be advantageously carried out using appropriate dehydrating agents such as $SOCl_2$, $POCl_3$, P_2O_5 , P_2S_5 , CS_2 and others.

25

The reaction may be carried out without solvent, or in a solvent including for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran

- 29 -

(THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

5 The reaction temperature is usually, but not limited to, about 10°C to 200°C and preferably about 50°C to 200°C. The reaction may be conducted for, usually, 10 minutes to 48 hours and preferably 30 minutes to 24 hours.

10 In the step 2, the compound of formula (II'') (wherein Y^1 , Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above, Y^2 and Y^3 independently represent CH or N and are connected by double bond) can be prepared, for example, from the compound of formula (II') (wherein Y^1 , Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above, Y^2 and Y^3 independently represent CR^3R^4 or NR^4 and are connected by single bond) by the oxidation reaction using an agent such as MnO_2 , $KMnO_4$ and others, or by the
15 dehydrogenation reaction using palladium on carbon.

The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; dimethyl-
20 formamide (DMF), dimethylacetamide (DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

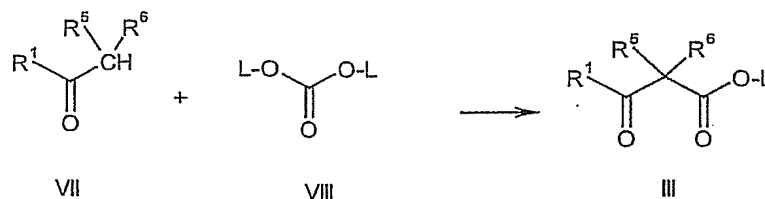
25 The reaction temperature is usually, but not limited to, about 0°C to 200°C and preferably about 50°C to 200°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 24 hours.

30 The compound of formula (VI) is commercially available or can be synthesized by conventional method.

- 30 -

The compound of formula (III) can be prepared, for example, by the following Method [A-ii].

Method [A-ii]



5 The compound of formula (III) (wherein L, R¹, R⁵ and R⁶ are the same as defined above) can be prepared by the reaction of the compound of formula (VII) (wherein R¹, R⁵ and R⁶ are the same as defined above) with the compound of formula (VIII) (wherein L is the same as defined above) in the presence of a base such as potassium hydride, potassium hexamethyldisilazide, and others.

10

The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene, dimethylformamide (DMF), dimethylacetamide(DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

15

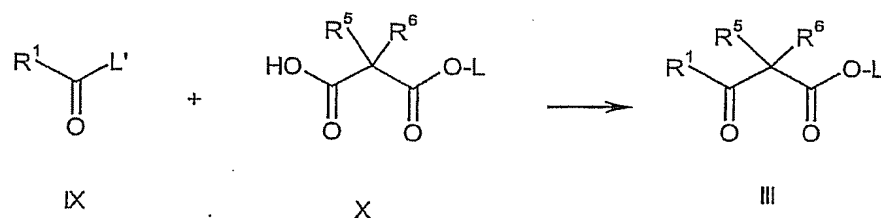
The reaction temperature is usually, but not limited to, about -100°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

20

Alternatively, the compound of formula (III) can be prepared, for example, by the following Method [A-iii].

- 31 -

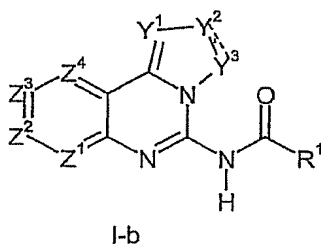
Method [A-iii]



The compound of formula (III) (wherein L, R¹, R⁵ and R⁶ are the same as defined above) can be prepared by the reaction of the compound of formula (IX) (wherein R¹ is the same as defined above and L' is a leaving group such as halogen atom e.g., chlorine or bromine atom, or imidazole) with the compound of formula (X) (wherein L, R⁵ and R⁶ are the same as defined above) or its salts, for example, potassium salt.

The reaction can be carried out in the presence of Lewis acid including magnesium salts, such as magnesium bromide, magnesium chloride, magnesium iodide, magnesium acetate, and others or a base such as n-butyl lithium, sec-butyl lithium, and others. The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

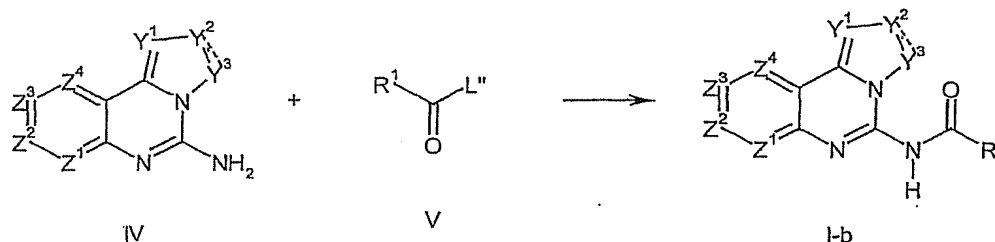
The preparation of the compound formula (I-b):



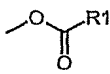
- 32 -

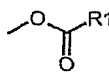
(wherein R^1 , Y^1 , Y^2 , Y^3 , Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above) can be, but not limited to be, prepared by the following Method B.

Method [B]



- 5 The compound of formula (I-b) can be prepared, for example, by the reaction of the compound of formula (IV) (wherein Y^1 , Y^2 , Y^3 , Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above) with a compound of formula (V) (wherein R^1 is the same as defined above and L'' is a leaving group, such as hydroxy; halogen atom e.g., chlorine, bromine, or iodine

- 10 atom; imidazole or,  wherein R^1 is the same as defined above). In the case L'' is hydroxy, the reaction can be advantageously carried out by using a coupling agent such as benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), 1,1'-carbonyldi(1,3-imiazole)(CDI), 1,1'-carbonyldi(1,2,4-triazole)(CDT) and others.

- 15 In the case L'' is halogen atom, imidazole, or  the reaction can be advantageously conducted in the presence of a base, including, for instance, such as pyridine, triethylamine and N,N-diisopropylethylamine, dimethylaniline, diethylaniline, and others.

- 20 The reaction may be carried out without solvent, or in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide

(DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

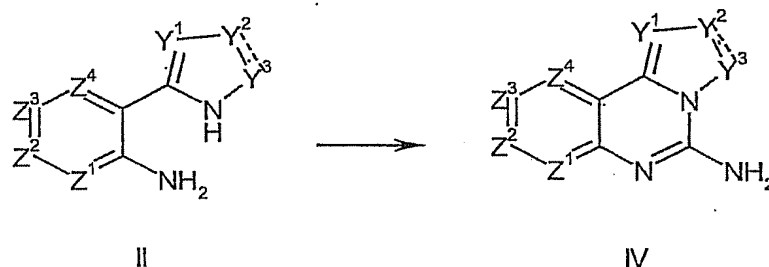
5

The reaction temperature is usually, but not limited to, about 40°C to 200°C and preferably about 20°C to 180°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

10 Preparation of intermediates

The compound of formula (IV) can be, but not limited to be, prepared by the following Method [B-i]:

Method [B-i]



15

The compound of formula (IV) (wherein Y^1 , Y^2 , Y^3 , Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above) can be prepared by the reaction of compound of formula (II) (wherein Y^1 , Y^2 , Y^3 , Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above) with cyanogen halides such as cyanogen bromide.

20

The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-

- 34 -

methylpyrrolidone; alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol; and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

- 5 The reaction temperature is usually, but not limited to, about -10°C to 200°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 hour to 24 hours.

- 10 The compound of formula (II) (wherein Y^1 , Y^2 , Y^3 , Z^1 , Z^2 , Z^3 and Z^4 are the same as defined above) can be obtained in the same manner described in Method [A-i].

The compound of formula (VII), (VIII), (IX) and (X) are commercially available or can be synthesized by conventional method.

- 15 When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon(s) in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

- 20 Typical salts of the compound shown by the formula (I) include salts prepared by the reaction of the compound of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

- 25 Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

- 30 Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal

- 35 -

hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tri(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salts thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring

- 36 -

agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

- 37 -

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from
5 about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxymethyl cellulose, low melting waxes, and cocoa butter.

10 Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and a sterile organic solvent.

15 The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

20 The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be
25 varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

30 Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01mg/kg/day to about 100mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In case of parenteral administration, it has generally proven

- 38 -

advantageous to administer quantities of about 0.001 to 100 mg/kg/day, preferably from 0.01 mg/kg/day to 1mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

5

- 39 -

Examples

5 The present invention will be described in detail below in the form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

10 ¹H NMR spectra were recorded using either Bruker DRX-300 (300 MHz for ¹H) spectrometer or Bruker 500 UltraShieldTM (500 MHz for ¹H). Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constant (J) are given in hertz and the abbreviations s, d, t, q, m, and br refer to singlet, doublet, triplet, quartet, multiplet, and broad,
15 respectively. The mass determinations were carried out by MAT95 (Finnigan MAT).

Liquid Chromatography - Mass spectroscopy (LC-MS) data were recorded on a Micromass Platform LC with Shimadzu Phenomenex ODS column(4.6 mm ϕ X 30 mm) flushing a mixture of acetonitrile-water (9:1 to 1:9) at 1 ml/min of the flow
20 rate. Mass spectra were obtained using electrospray (ES) ionization techniques (Micromass Platform LC). TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150 μ m)) was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Tokyo kasei
25 kogyo Co., Ltd., Nacalai tesque, Inc., Watanabe Chemical Ind. Ltd., Maybridge plc, Lancaster Synthesis Ltd., Merck KGaA, Kanto Chemical Co., Ltd.

The effects of the compounds of the present invention were examined by the following assays.

30

- 40 -

[Determination of IC₅₀ values of compounds in kinase assay of PI3K γ]

Chemicals and assay materials

Phosphatidylinositol (PtdIns) and phosphatidylserine (PtdSer) were purchased from
5 DOOSAN SERDARY RESEARCH LABORATORIES (Toronto, Canada). Recombinant
human PI3K γ (full length human PI3K p110 γ fused with a His₆-tag at the C-terminus
expressed in *S. frugiperda* 9 insect cells) was obtained from ALEXIS BIOCHEMICALS
(#201-055-C010; San Diego, CA). [γ ³³P]ATP and unlabeled ATP were purchased
from AMERSHAM PHARMACIA BIOTECH (Buckinghamshire, UK) and ROCHE
10 DIAGNOSTICS (Mannheim, Germany), respectively. Scintillation cocktails and
MicroScint PSTM were purchased from PACKARD (Meriden, CT). MaxisorpTM plates
were purchased from NALGE NUNC INTERNATIONAL K.K. (Tokyo, Japan). All other
chemicals not further specified were from WAKO PURE CHEMICALS (Osaka, Japan).

15 *Solid-Phase Lipid Kinase Assay*

To assess inhibition of PI3K γ by compounds, the MaxisorpTM plates were coated
with 50 μ l/well of a solution containing 50 μ g/ml PtdIns and 50 μ g/ml PtdSer
dissolved in chloroform:ethanol (3:7). The plates were subsequently air-dried by
20 incubation for at least 2 hours in a fume hood. The reaction was set up by mixing
25 μ l/well of assay buffer 2x (100 mM MOPSO/NaOH, 0.2 M NaCl, pH 7.0, 8 mM
MgCl₂, 2 mg/ml BSA (fatty acid-free)) and 50 ng/well PI3K γ in the lipid pre-coated
plate and 10x test compounds were added in 2% DMSO. The reaction was started by
adding 20 μ l/well of ATP mix (final 10 μ M ATP; 0.05 μ Ci/well [γ ³³P]ATP). After
25 incubation at RT for 2 hours, the reaction was terminated by adding 50 μ l/well stop
solution (50 mM EDTA, pH 8.0). The plate was then washed twice with Tris-
buffered saline (TBS, pH 7.4). MicroScint PSTM (PACKARD) scintillation mix was
added at 100 μ l/well, and radioactivity was counted by using a TopCountTM
(PACKARD) scintillation counter.

30

- 41 -

The inhibition percent at each concentration of compound was calculated, and IC50 values were determined from the inhibition of curve.

[Isozyme selectivity test in PI3K]

5

{Determination of IC50 values of compounds in kinase assay of PI3K β }

Recombinant baculovirus of PI3K β p110 β and GST-p85 α were obtained from Dr. Katada (University of Tokyo). Recombinant PI3K heterocomplex of p110 β and
10 GST-p85 α were co-expressed in insect cells according to manufacture's instruction (Pharmingen, San Diego, CA), and purified with glutathione affinity column. Kinase assay of PI3K β was prepared in a similar manner as described in the part of [Determination of IC50 values of compounds in kinase assay of PI3K γ].

15

[Selectivity test with other kinases]

Kinase selectivity of the compounds was assessed by using a few kinase assays such as kinase assay of Syk.

20

{Syk tyrosine kinase inhibitory assay for selectivity}

(1) Preparation of Syk protein

A cDNA fragment encoding human Syk openreading frame was cloned from total
25 RNA of human Burkitt's lymphoma B cell lines, Raji (American Type Culture Collection), with the use of RT-PCR method. The cDNA fragment was inserted into pAcG2T (Pharmingen, San Diego, CA) to construct a baculovirus transfer vector. Then the vector, together with the linearized baculovirus (BaculoGoldTM, Pharmingen), was used to transfect Sf21 cells (Invitrogen, San Diego, CA).

30

- 42 -

Generated recombinant baculovirus was cloned and amplified in Sf21 cells. Sf21 cells were infected with this amplified high titer virus to produce a chimeric protein of Syk kinase fused by glutathione-S-transferase (GST).

5 The resulting GST-Syk was purified with the use of glutathione column (Amersham Pharmacia Biotech AB, Uppsala, Sweden) according to the manufacturer's instruction. The purity of the protein was confirmed to be more than 90% by SDS-PAGE.

10 (2) Synthesize of a peptide

Next, a peptide fragment of 30 residues including two tyrosine residues, KISDFGLSKALRADENYYKAQTHGKWPVKW, was synthesized by a peptide synthesizer. The N-terminal of the fragment was then biotinylated to obtain
15 biotinylated activation loop peptide (AL).

(3) The measurement of Syk tyrosine kinase activity

All reagents were diluted with the Syk kinase assay buffer (50 mM Tris-HCl (pH
20 8.0), 10 mM MgCl₂, 0.1 mM Na₃VO₄, 0.1% BSA, 1 mM DTT). First, a mixture (35 µl) including 3.2 µg of GST-Syk and 0.5 µg of AL was put in each well in 96-well plates. Then 5 µl of a test compound in the presence of 2.5% dimethyl sulfoxide (DMSO) was added to each well. To this mixture was added 300 µM ATP (10 µl) to initiate the kinase reaction. The final reaction mixture (50 µl) consists of 0.65 nM
25 GST-Syk, 3 µM AL, 30 µM ATP, a test compound, 0.25% DMSO, and a Syk kinase assay buffer.

The mixture was incubated for 1 hour at room temperature (RT), and the reaction was terminated by the addition of 120 µl of termination buffer (50 mM Tris-HCl (pH
30 8.0), 10 mM EDTA, 500 mM NaCl, 0.1% BSA). The mixture was transferred to streptavidin-coated plates and incubated for 30 minutes. at room temperature to

- 43 -

combine biotin-AL to the plates. After washing the plates with Tris-buffered saline (TBS) (50 mM Tris-HCl (pH 8.0), 138 mM NaCl, 2.7 mM KCl) containing 0.05% Tween-20 for 3 times, 100 μ l of antibody solution consisting of 50 mM Tris-HCl (pH 8.0), 138 mM NaCl, 2.7 mM KCl, 1% BSA, 60 ng/ml anti-phosphotyrosine monoclonal antibody, 4G10 (Upstate Biotechnology), which was labeled with europium by Amersham Pharmacia's kit in advance, was added and incubated at room temperature for 60 minutes. After washing, 100 μ l of enhancement solution (Amersham Pharmacia Biotech) was added and then time-resolved fluorescence was measured by multi-label counter ARVO (Wallac Oy, Finland) at 340 nm for excitation and 615 nm for emission with 400 msec of delay and 400 msec of window.

[Determination of IC₅₀ values of compounds in superoxide generation from human peripheral mononuclear cells]

Blood (100 ml/donor) was taken from healthy human volunteers by venepuncture with 50 ml syringes containing 50 units heparin. Red blood cells were removed by incubation with 1% (w/v) dextran and 0.45% (w/v) glucose for 30 minutes at room temperature. After centrifugation at 350 xg for 10 minutes, the cell pellet was resuspended in 10 ml PBS. The cell suspension was gently layered on 20 ml of 60% and 20ml of 80% Percoll (Amersham Pharmacia Biotech, Sweden) gradient in PBS in 50 ml tube (#2335-050, Iwaki, Japan). After centrifugation at 400 xg for 30 minutes at room temperature, peripheral polymorphonuclear leukocytes (PMNs) were obtained from the interference between 60% and 80% Percoll phases. After twice washing in PBS, PMNs were suspended at a density of 10^7 cells/ml in Hank's Balanced Salt Solution (HBSS: Nissui, Japan) supplemented by 10 mM Na-Hepes (pH 7.6), 0.1% BSA and kept on ice until further use.

To test inhibition of formyl-methionyl-leucyl-phenylalanine (fMLP)-induced superoxide generation by compounds, PMNs (2×10^5 cells/well) were seeded in HBSS, 10 mM Na-Hepes (pH 7.6), 0.1% BSA in 96-well clear bottom black plate (Cat.#3904, Costar) and pretreated with luminol (1 μ g/well; Sigma) and test

- 44 -

compounds for 10 minutes at 37°C. fMLP peptide (Cat.#4066; Peptide Institute Inc, Japan) was prepared in 10 μ M in the same buffer and prepared in a polypropylene plate (Cat.#3365, Coster). Chemiluminescence (CL) was measured by FDSS-6000 (Hamamatsu Photonics) over 15 minutes after stimulation with 1 μ M fMLP. The percentage of inhibition at each concentration of compound was calculated based on the first peak of CL at approximately 1 minute after addition of stimulus and IC50 values were determined from the inhibition curve.

For opsonized zymosan (OZ) and phorbol 12-myristate 13-acetate (PMA) stimulation, Zymosan A (Sigma) was suspended in HBSS at a concentration of 1 mg/ml and incubated with human pooled serum at a final concentration range of 9 to 80% at 37°C for 30 minutes to opsonize the zymosan, followed by centrifugation at 500 \times g for 10 minutes at 4°C. Then the sediments were washed twice in HBSS and finally resuspended in HBSS to a concentration between 1 and 10 mg/ml. Opsonized zymosan (OZ) was used at 5 mg/ml for stimulation. Phorbol12-myristate 13-acetate (PMA) was initially dissolved at a concentration of 0.1 mg/ml in DMSO as a stock solution and stored frozen at -20°C. PMA solution was prepared from the stock solution by further dilution in HBSS to the concentration of 100 ng/ml. PMNs (2 x 10⁵ cells/well) were seeded in HBSS, 10 mM Na-Hepes (pH 7.6), 0.1% BSA in 96-well white plate (Packard) and pretreated with luminol (1 μ g/well; Sigma) and test compounds for 10 minutes at 37°C. CL was measured by Arvo counter (Wallac)) at 30 minutes after the stimulation with OZ or PMA. The percentage of inhibition at each concentration of compound was calculated and IC50 values were determined from the inhibition curve.

25

[Determination of IC50 values of compounds in elastase release from human peripheral mononuclear cells]

30

To test inhibition of elastase release by compounds, PMNs (5 x 10⁵ cells/well) were seeded in HBSS supplemented with 10 mM Na-Hepes (pH 7.6), 0.1% BSA in 96-well plate. Cells were pretreated with cytochalasine B (0.1 μ g/well; Nakarai, Japan).

- 45 -

and test compounds in 90 μ l/well for 10 minutes at 37°C. Cells were stimulated with 1 μ M fMLP for 15 minutes at 37°C. Supernatants (40 μ l/well) were collected into 384 well black plate (Packard) to measure elastase activity. Fluorescent-based elastase reaction was started by the addition of 10 μ l of 0.5 mM Suc-Ala-Ala-Ala-MCA (Cat. #3133v; Peptide Institute Inc, Japan) into the 384 well plate at room temperature. The fluorescence emission was measured at 460 nm (λ_{ex} , 360 nm) by using a Wallac-Arvo counter (PerkinElmer, Boston, MA) fluorescence plate reader for 120 minutes. IC50 values of compounds were determined at the initial velocity of the reaction.

10

[Determination of IC50 values of compounds in chemotaxis assay with the use of human PMNs]

15

Freshly prepared PMNs (1.1×10^7 cells/ml) were incubated with compounds in a polypropylene 96 well plate (Cat.#3365, Coster) for 10 minutes in HBSS supplemented with 10 mM Na-Hepes (pH 7.6), 0.1% BSA. Cells (100 μ l) were incubated with test compounds or vehicle for 30 minutes and were transferred into an Multiwell insert (Cat.# 351183; Falcon) 24w plate. FMLP (10 nM, 0.5 ml) was added into the lower chamber of the plate, and chemotaxis was measured in CO₂ incubator at 37°C for 1 hour. Migrated cells were counted using FACScan (Becton Dickinson, Franklin Lakes, NJ). The percentage of inhibition at the each concentration of compound was calculated, and the IC50 values were determined from the inhibition curve.

20

25

[Determination of IC50 values of compounds in chemotaxis assay with the use of transfectants]

(1) cell

30

Human CCR3-transformed L1.2 cells were used. Human CCR3-expressing L1.2 stable transformant was established by electroporation, referring to the methods described in J. Exp. Med. 183:2437-2448, 1996. The human CCR3-transformed L1.2

- 46 -

cells were maintained in RPMI-1640 supplemented with 10% FCS , 100 units/ml of penicillin G and 100 µg/ml of streptomycin, and 0.4 mg/ml of Geneticin. One day before the chemotaxis assay, cells were pretreated with 5 mM sodium butyrate - containing culture medium (5×10^5 cells/ml) for 20-24 hours to increase the expression of CCR3.

(2) Chemotaxis assay

Butyrate-pretreated cells were suspended in chemotaxis buffer (Hanks' solution Cat.#05906 Nissui, 20 mM HEPES pH 7.6, 0.1% human serum albumin Cat.#A-1887 Sigma) at a cell density of 1.1×10^7 cells /ml. A mixture of 90 µl of cell suspension and 10 µl of compound solution diluted with chemotaxis buffer (10-times concentration of the final concentration) were preincubated for 10 minutes at 37°C. The mixture of cells and compounds was added into the upper chamber of the 24-well chemotaxis chamber (Transwell™, Cat.#3421, Costar, pore size; 5 µm). 0.5 ml of 10 nM of human recombinant eotaxin (Cat.#23209, Genzyme Techne) solution, diluted with chemotaxis buffer, was added into the lower chamber of the chemotaxis plate. Then, chemotaxis was performed in CO₂ incubator at 37°C for 4 hours. After 4 hours incubation, migrated cells were counted using FACScan (Becton Dickinson). The percentage of inhibition at the each concentration of compound was calculated, and IC₅₀ values were determined from the inhibition curve.

[Mouse fMLP-induced pleurisy Model]

Seven weeks old BALB/c female mice were divided into 3 groups, a nontreatment group, a vehicle group and a treatment group. Mice in the treated group were first injected intravenously with compounds of the present invention at varied doses. Mice in the vehicle group were injected with vehicle containing 10% Cremophor EL (Nacalai Tesque) in saline. Three minutes after the treatment, a solution containing 1 mg/mouse of fMLP in 3.3% DMSO in PBS was administrated intrapleurally into a vehicle group and a treated group mice. Four hours after fMLP-injection, mice were

- 47 -

sacrificed and pleural fluid was collected by washing the pleural cavity twice with 2 ml PBS. Total cells per milliliter of pleural fluid were counted using a hemacytometer. Cell differentiation of pleural fluid was determined by counting a minimum of 200 cells from a Giemsa's-stained cytospin slide preparation. Statistical analysis was performed by means of Student's t-test for paired data or analysis of variance with Dunnett's Post test, using GraphPadPRISM for Windows, version 2.01.

For practical reasons, the compounds are grouped in some classes of activity as follows:

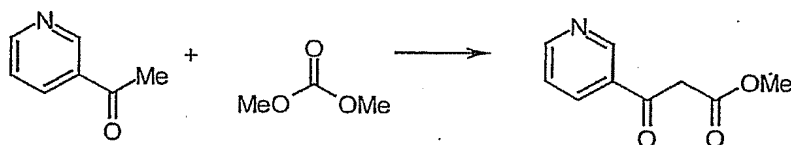
In vitro $IC_{50} = A (= \text{or } <) 0.1 \mu M < B (= \text{or } <) 0.5 \mu M < C (= \text{or } <) 2 \mu M < D$

The compounds of the present invention also show strong activity in vivo assays. (dec.) in the following tables represents decomposition.

Example 1-1:

Z)-2-(8,9-Dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethanol

(1) Methyl 3-oxo-3-(3-pyridinyl)propanoate

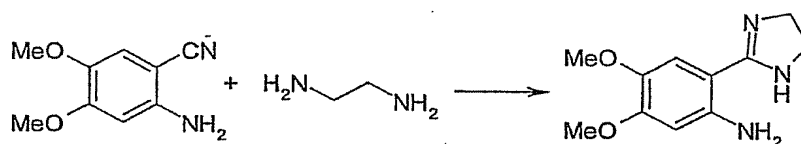


A 0.5 M solution of potassium hexamethyldisilazide in toluene (22 ml, 11 mmol) was mixed with tetrahydrofuran (5 ml), and the mixture was cooled at -78°C . To the cold (-78°C) mixture was added dropwise a solution of 3-acetylpyridine (1.0 g, 8.26 mmol) in tetrahydrofuran (5 ml). The mixture was warmed to room temperature

- 48 -

and stirred for 3 hours. The mixture was cold at -78°C , and then dimethyl carbonate (1.2 ml, 14.3 mmol) was added dropwise. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction solution was quenched by adding aqueous 1N HCl solution, and extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtrated, and concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel (hexane/ ethyl acetate, 1/1) to give methyl 3-oxo-3-(3-pyridinyl)propanoate (1.0 g, 68% yield) as an oil.

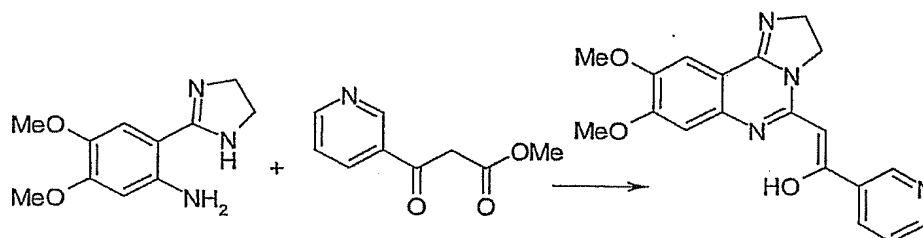
10 (2) 2-(4,5-Dihydro-1H-imidazol-2-yl)-4,5-dimethoxyaniline:



2-Amino-4,5-dimethoxybenzonitrile (5.0 g, 28 mmol) was added to ethylenediamine (7.9 g, 131 mmol) at room temperature. The resulting solution was warmed to 40°C , and a catalytic amount of diphosphorus pentasulfide (50 mg) was added. The mixture was heated to $80-90^{\circ}\text{C}$, and the stirring was continued overnight. The reaction mixture was diluted with water, and the resulting precipitate was collected by filtration to give 2-(4,5-dihydro-1H-imidazol-2-yl)-4,5-dimethoxyaniline (5.1 g, 82 %) as a solid.

20

(3) (Z)-2-(8,9-Dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethanol



- 49 -

A mixture of 2-(4,5-dihydro-1H-imidazol-2-yl)-4,5-dimethoxyaniline (0.15 g, 0.68 mmol) and methyl-3-oxo-3(3-pyridinyl)propanoate (0.20 g, 1.12 mmol) was stirred at 155. for 1 hour. The reaction mixture was purified by column chromatography on silica-gel (dichloromethane/ methanol, 25/1) to give (Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl) ethenol (66.9mg, 28%) as a yellow solid.

Melting point: 275°C

Mass spectrometry: 351

10 In vitro PI3K- β inhibitory activity: C

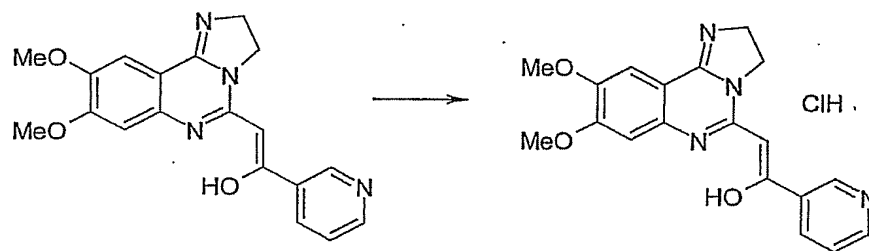
In vitro PI3K- γ inhibitory activity: A

¹H-NMR (500 MHz, DMSO-d₆): δ 3.79 (3H, s), 3.88 (3H, s), 3.98-4.08 (4H, m), 5.63 (1H, s), 7.13 (1H, s), 7.24 (1H, s), 7.50 (1H, dd, J = 4.7, 7.8 Hz), 8.27 (1H, dt, J = 1.6, 7.8 Hz), 8.67 (1H, dd, J = 1.6, 4.7 Hz), 9.13 (1H, d, J = 1.6 Hz), 13.9 (1H, bs).

Example 1-2:

(Z)-2-(8,9-Dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)-ethenol hydrochloride

20



To a solution of (Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethenol (16.8 mg, 0.05 mmol) in dioxane (15 ml) at room temperature was added aqueous 6N HCl solution (0.05 ml). After being stirred for 30 minutes, the mixture was dried under reduced pressure to give (Z)-2-(8,9-dimethoxy-2,3-di-

25

- 50 -

hydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethenol hydrochloride (18.5 mg, quantitative) as a yellow solid.

Melting point: >300°C

5 Mass spectrometry: 351

In vitro PI3K- β inhibitory activity: C

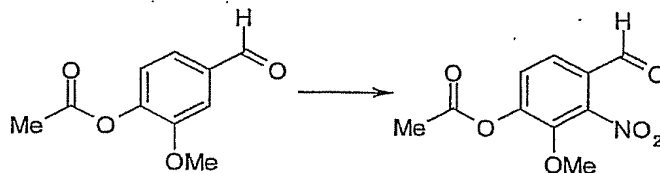
In vitro PI3K- γ inhibitory activity: A

10 $^1\text{H-NMR}$ (500 MHz, DMSO- d_6): δ 3.88 (3H, s), 4.00 (3H, s), 4.22 (2H, t, $J = 9.1$ Hz), 4.55 (2H, t, $J = 9.1$ Hz), 6.21 (1H, s), 7.60 (1H, s), 7.66 (1H, dd, $J = 4.7, 8.2$ Hz), 7.90 (1H, s), 8.47 (1H, d, $J = 8.2$ Hz), 8.79 (1H, d, $J = 4.7$ Hz), 9.28 (1H, s), 14.9 (1H, bs).

Example 1-3:

15 2-[7-Methoxy-8-(methoxymethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol

(1) 4-Formyl-2-methoxy-3-nitrophenyl acetate



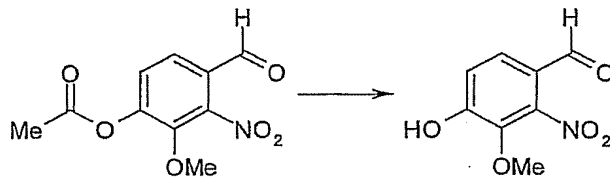
20 By the procedure described in US Patent 4287341 or J. Chem. Soc. 376 (1948), vanillin acetate 5.00g afforded the title compound 4.54g as yellow solid. Yield 73.6%.

$^1\text{H-NMR}$ (500MHz, DMSO- d_6) δ : 2.40(s 3H), 3.87(s 3H), 7.75(d 1H $J=8.4\text{Hz}$), 7.94(d 1H $J=8.4\text{Hz}$), 9.90(s 1H)

25

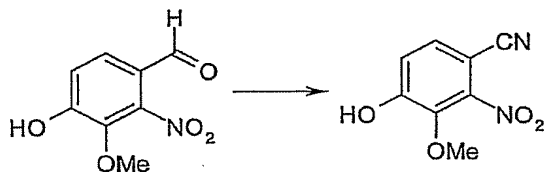
- 51 -

(2) 4-Hydroxy-3-methoxy-2-nitrobenzaldehyde



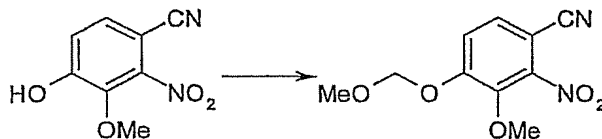
A mixture of 4-formyl-2-methoxy-3-nitrophenyl acetate 4.54g (19.0mmol) and potassium carbonate 5.24g (37.9mmol) in methanol 40mL was stirred at room temperature for 2 hours. The reaction mixture was poured into water, acidified by 1N HCl solution and extracted into AcOEt. The organic layer was washed with brine, dried over MgSO₄, filtrated and the solvent was evaporated. The residue was washed with n-hexane to give the title compound 3.60g as white solid. Yield 96.3%.

10 (3) 4-Hydroxy-3-methoxy-2-nitrobenzonitrile



To a mixture of 4-hydroxy-3-methoxy-2-nitrobenzaldehyde 14.5g (73.5mmol) in 28% ammonia solution 150mL and tetrahydrofuran 15mL was added iodine 22.4g (88.2mmol) and stirred at room temperature for overnight. The reaction mixture was concentrated in vacuo. The residue was acidified with 2H HCl solution and extracted into diethyl ether. The organic layer was washed with brine, dried over MgSO₄, filtrated and the solvent was evaporated. The residue was washed with diisopropyl ether to give the title compound 12.1g as brown solid. Yield 84.5%

20 (4) 3-Methoxy-4-(methoxymethoxy)-2-nitrobenzonitrile

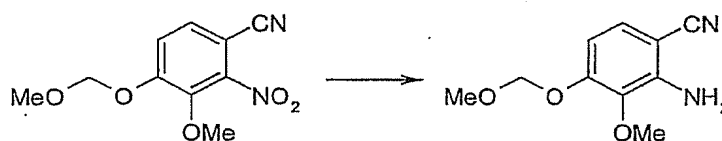


A mixture of 4-hydroxy-3-methoxy-2-nitrobenzonitrile 1.00g, chloromethyl methyl ether 0.47mL (6.18mmol) and potassium carbonate 3.56g (25.8mmol) in N,N-

- 52 -

dimethylformamide 10mL was stirred at 50°C for 2 hours. The reaction mixture was poured into water and extracted into diethyl ether. The organic layer was washed with brine, dried over MgSO₄, filtrated and the solvent was evaporated. Silica gel chromatography (n-hexane / AcOEt = 4/1) afforded the title compound 1.03g as colorless solid. Yield 83.5%.

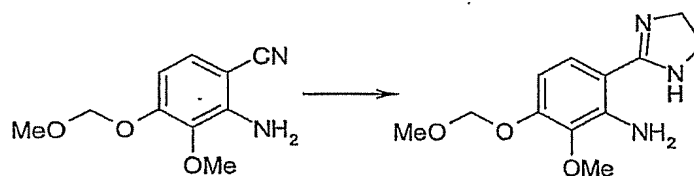
(5) 2-Amino-3-methoxy-4-(methoxymethoxy)benzonitrile



To 5% palladium on activated carbon 6.00g under argon atmosphere was added a solution of 3-methoxy-4-(methoxymethoxy)-2-nitrobenzonitrile 6.00g (25.2mmol) in ethanol 50mL and stirred under hydrogen atmosphere at room temperature for 8 hours. The reaction mixture was filtrated and the filtrate was concentrated in vacuo. Silica gel chromatography (n-hexane / AcOEt = 4/1) afforded the title compound 2.83g as white solid. Yield 53.9%.

15

(6) [6-(4,5-Dihydro-1H-imidazol-2-yl)-2-methoxy-3-(methoxymethoxy)phenyl]amine

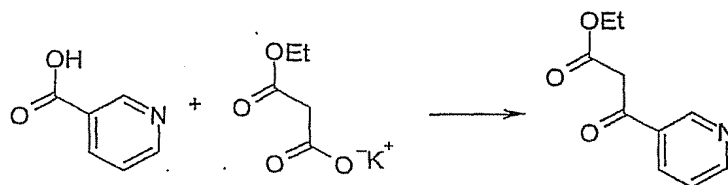


A solution of 2-amino-3-methoxy-4-(methoxymethoxy)benzonitrile 475mg (2.28mmol) and phosphorus pentasulfide 25.4mg (0.11mmol) in ethylenediamine 2.75g was stirred at 120°C for overnight. The reaction mixture was cooled to room temperature and poured into water. The precipitate was collected and washed with water to give the title compound 293mg as white solid. Yield 51.1%.

25

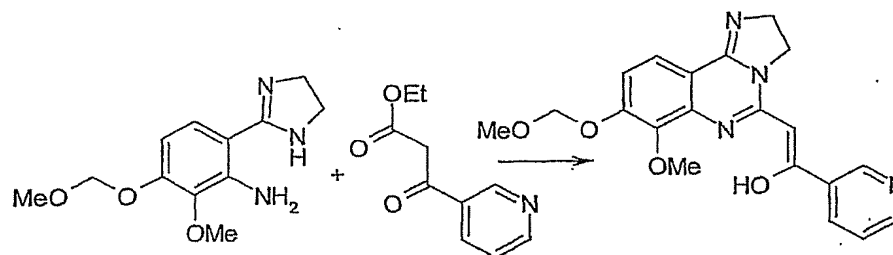
(7) Ethyl 3-oxo-3-(pyridin-3-yl)propanoate

- 53 -



To a suspension of nicotinic acid 5.00g (40.6mmol) in tetrahydrofuran 50mL was added carbonyl diimidazole 9.76g (60.9mmol) at 5°C and stirred at room temperature for 1 hour. In a separate flask, a suspension of MgCl_2 4.64g (48.7mmol) and ethyl malonate potassium salt 10.37g (60.92mmol) in tetrahydrofuran 50mL was stirred at 50°C for 4 hours. To this suspension was added the aforementioned imidazolidine solution at room temperature and stirred for 12 hours. The reaction was quenched by the addition of water and extracted into ethyl acetate. The organic layer was washed by brine, dried over MgSO_4 , filtrated and the solvent was evaporated. Silica gel chromatography (n-hexane / AcOEt = 2/1) afforded the title compound 3.89g as pale yellow oil. Yield 49.5%.

(8) 2-[7-Methoxy-8-(methoxymethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol



A solution of [6-(4,5-dihydro-1H-imidazol-2-yl)-2-methoxy-3-(methoxymethoxy)phenyl]amine 1.31g (5.20mmol) and ethyl 3-oxo-3-(pyridin-3-yl)propanoate 1.00g (5.20mmol) in toluene 30mL was refluxed for overnight. The precipitate was collected and washed with diethyl ether to give the title compound 1.52g as a yellow solid. Yield 76.9%.

Melting point: 215-216°C

Mass spectrometry: 381

- 54 -

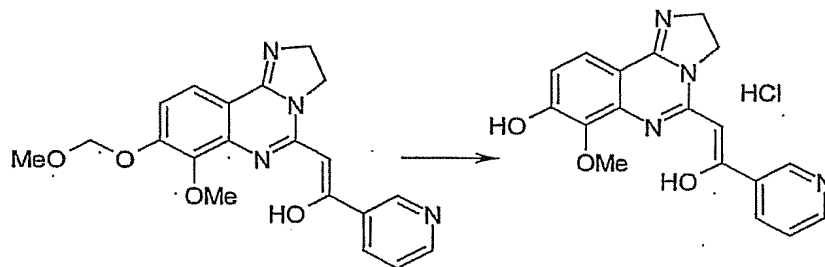
In vitro PI3K- β inhibitory activity:

In vitro PI3K- γ inhibitory activity: B

5 H-NMR (500MHz, CDCl_3) δ : 3.54(s 3H), 3.95(t 2H $J=9.5\text{Hz}$), 4.08(s 3H), 4.22(t 2H $J=9.5\text{Hz}$), 5.30(s 2H), 5.38(s 1H), 6.98(d 1H $J=8.8\text{Hz}$), 7.37(dd 1H $J=8.0\text{Hz}$, 4.9Hz), 7.64(d 1H $J=8.8\text{Hz}$), 8.21(dt 1H $J=8.0\text{Hz}$, 1.7Hz), 8.67(dd 1H $J=4.9\text{Hz}$, 1.7Hz), 9.09(d 1H $J=1.7\text{Hz}$), 13.75(s 1H)

Example 1-4:

10 5-(2-Hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-ol hydrochloride



A suspension of 2-[7-methoxy-8-(methoxymethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethanol (Example 1-3) 1.52g (4.00mmol) in 4N HCl in 1,4-dioxane 30mL and water 0.3mL was stirred at room temperature for overnight. The reaction mixture was diluted with diethyl ether. The precipitate was collected and washed with diethyl ether to give the title compound 1.23g as a yellow solid. Yield 82.4%

20 Melting point: 245°C

Mass spectrometry: 337

In vitro PI3K- β inhibitory activity: C

In vitro PI3K- γ inhibitory activity: A

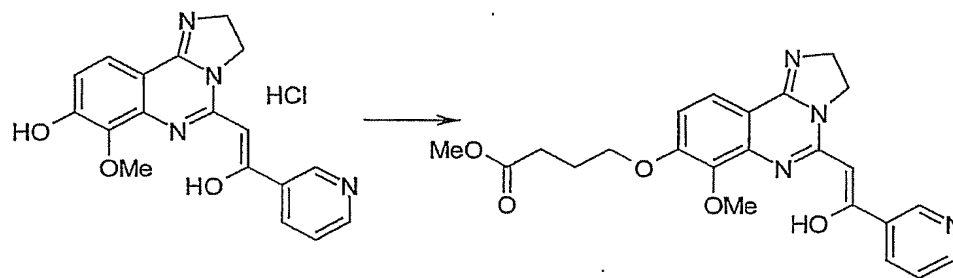
25 H-NMR (500MHz, DMSO-d_6) δ : 3.97(s 3H), 4.22(dd 2H $J=12.3\text{Hz}$, 9.0Hz), 4.43(dd 2H $J=12.3\text{Hz}$, $J=9.0\text{Hz}$), 6.17(s 1H), 7.10(d 1H $J=9.0\text{Hz}$), 7.71(dd 1H

- 55 -

J=7.7Hz, 4.7Hz), 7.98(d 1H J=9.0Hz), 8.57(br d 1H J=7.7Hz), 8.82 (dd 1H J=4.7Hz, 1.4Hz), 9.34(d 1H J=1.4Hz), 11.79(s 1H), 14.60(s 1H)

Example 1-5:

5 Methyl 4-{[5-(2-hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl]oxy}butanoate



A mixture of 5-(2-hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-ol hydrochloride (Example 1-4) 50.4mg (0.14mmol), methyl chloro-
 10 butyrate 22.2mg (0.16mmol) and potassium carbonate 186.9mg (1.35mmol) in N,N-dimethylformamide 1mL was stirred at 120°C for 4 hours. The reaction mixture was poured into water and extracted into dichloromethane. The organic layer was washed with brine, dried over MgSO₄, filtrated and the solvent was evaporated. The residue was washed by diethyl ether to give the title compound 35.0mg as yellow solid. Yield 59.3%.

Melting point: 199-200°C

Mass spectrometry: 437

In vitro PI3K-β inhibitory activity: C

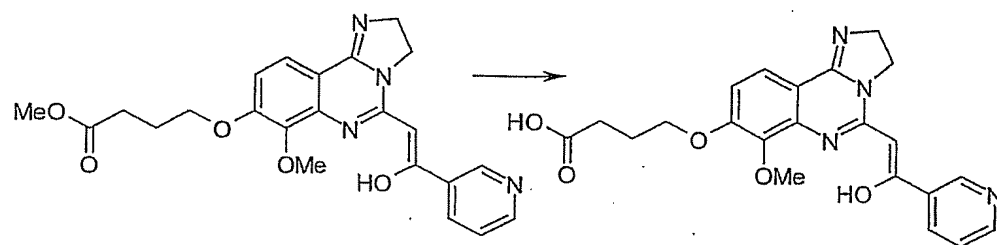
20 In vitro PI3K-γ inhibitory activity: A

H-NMR (500MHz, CDCl₃) δ: 2.20(quint 2H J=7.1Hz), 2.58(t 2H J=7.09Hz), 3.71(s 3H), 3.94(t 2H J=9.5Hz), 4.06(s 3H), 4.15(t 2H J=7.1Hz), 4.21(t 2H J=9.5Hz), 5.38(s 1H), 6.76(d 1H J=8.8Hz), 7.37(dd 1H J=8.2Hz, 5.2Hz), 7.65(d 1H J=8.8Hz), 8.21(dt J=8.2Hz, 2.1Hz), 8.67(d 1H J=5.2Hz), 9.09(s 1H), 13.70(s 1H)

- 56 -

Example 1-6:

Example 3-4; 4-[[5-(2-Hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl]oxy}butanoic acid



5 A solution of methyl 4-[[5-(2-hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl]oxy}butanoate (example 1-5) 20.0mg (0.05mmol) in 1N LiOH solution 0.1mL and ethanol 1.0mL was stirred at room temperature for overnight. The reaction mixture was neutralized with 1N HCl solution and concentrated in vacuo. The residue was triturated in water. The precipitate was
10 collected to give the title compound 10.0mg as white solid. Yield 51:7%.

Melting point: 257-258°C

Mass spectrometry: 423

In vitro PI3K-β inhibitory activity: B

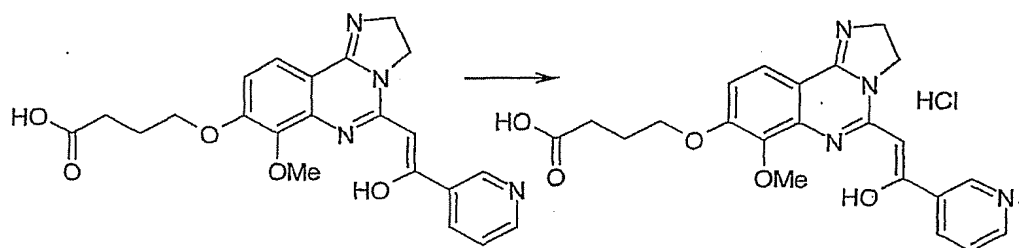
15 In vitro PI3K-γ inhibitory activity: A

H-NMR (500MHz, DMSO-d₆) δ: 2.02(quint 2H J=6.2Hz), 2.45(t 2H J=6.2Hz), 3.94(s 3H), 3.98(br t 2H J=8.5Hz), 4.06(br t 2H J=8.5Hz), 4.14(t 2H J=6.2Hz), 5.67(s 1H), 6.97(d 1H J=8.7Hz), 7.49(dd 1H J=8.2Hz, 4.4Hz), 7.57(d 1H J=8.7Hz), 8.29(d
20 1H J=8.2Hz), 8.67(d 1H J=4.4Hz), 9.14(s 1H), 12.15(s 1H), 13.76(s 1H)

Example 1-7:

4-[[5-(2-Hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl]oxy}butanoic acid hydrochloride

- 57 -



A mixture of 4-[[5-(2-hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl]oxy]butanoic acid (Example 1-6) 4.0mg (9.5micromol) in 4N HCl in 1,4-dioxane 2.0mL was stirred at room temperature for 2 hours. The reaction mixture was diluted with diethyl ether. The precipitate was collected to give the title compound 4.00mg as a yellow solid. Yield 92.0%.

Melting point: 249-251°C

Mass spectrometry: 423

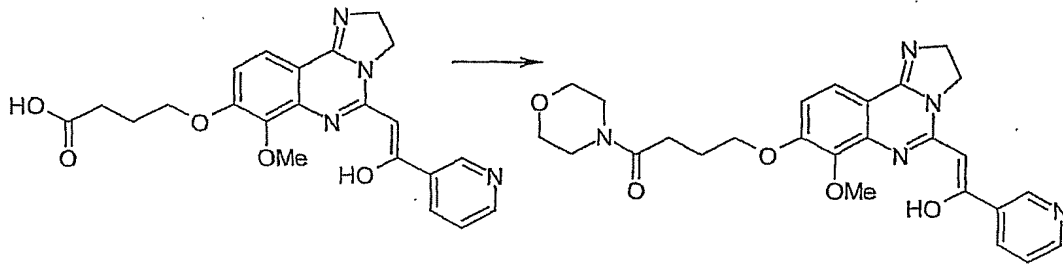
In vitro PI3K- β inhibitory activity: B

In vitro PI3K- γ inhibitory activity: A

¹H-NMR (500MHz, DMSO-d₆) δ : 2.06(quint 2H J=7.3Hz), 2.46(t 2H J=7.3Hz), 4.01(s 3H), 4.24(t 2H J=9.0Hz), 4.29(t 2H J=7.3Hz), 4.45(t 2H J=9.0Hz), 6.18(s 1H), 7.36(d 1H J=9.1Hz), 7.70(dd 1H J=7.9Hz, 5.0Hz), 8.14(d 1H J=9.1Hz), 8.56(br d 1H J=7.9Hz), 8.82(br d 1H J=5.0Hz), 9.34(s 1H), 12.34(s 1H), 14.57(s 1H)

Example 1-8:

2-[7-Methoxy-8-(4-morpholin-4-yl-4-oxobutoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol



- 58 -

To a solution of 4-{{[5-(2-hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl]oxy}butanoic acid (Example 1-6) 20.0mg (0.044mmol), morpholine 19.0mg (0.22mmol) and N,N-diisopropylethylamine 0.038mL (0.22mmol) in N,N-dimethylformamide 2.0mL was added PyBOP((1H-1,2,3-benzotriazol-1-yloxy)(tripyrrolidin-1-yl)phosphonium hexafluorophosphate) 34.0mg (0.065mmol) and stirred at 80°C for overnight. After cooling to room temperature, the reaction mixture was poured into water. The precipitate was collected and washed with water to give the title compound 13.0mg as a white solid. Yield 60.7%.

10 Melting point: 234-235°C

Mass spectrometry: 492

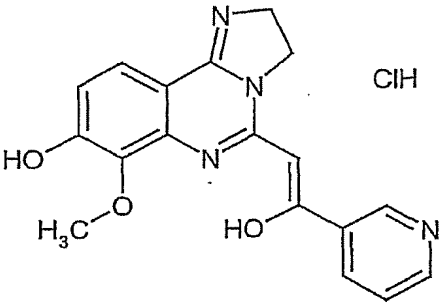
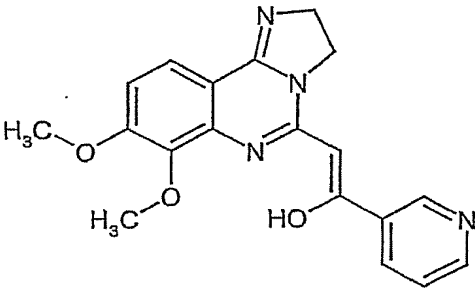
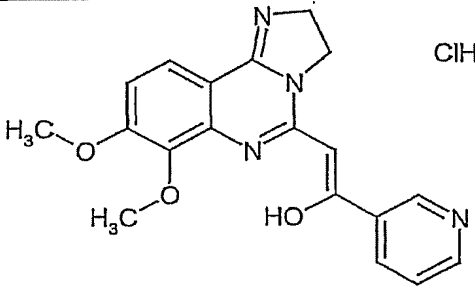
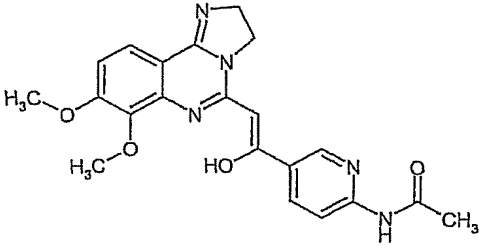
In vitro PI3K- β inhibitory activity: B

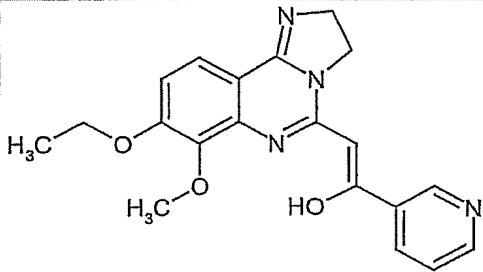
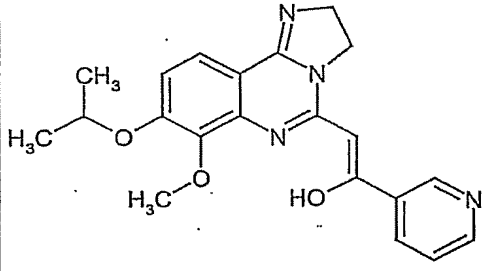
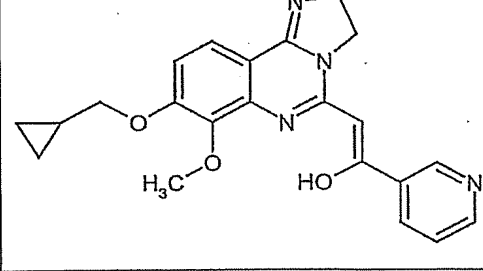
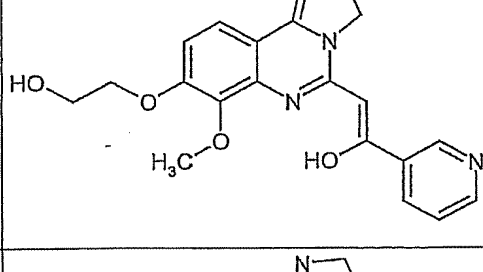
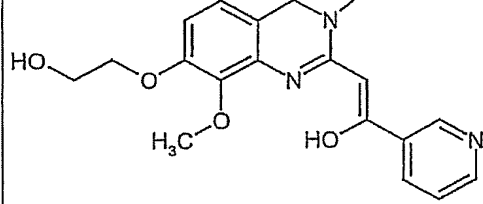
In vitro PI3K- γ inhibitory activity: A

15 ¹H-NMR (500MHz, DMSO-d₆) δ : 2.03 (quint 2H J=6.6Hz), 3.46 (m 4H), 3.56 (m 4H), 3.96 (s 3H), 3.99 (br d 2H J=8.2Hz), 4.05 (br d 2H J=8.2Hz), 4.15 (t 2H J=6.6Hz), 5.66 (s 1H), 6.98 (d J=8.8Hz), 7.50 (dd 1H J=7.7Hz, 4.7Hz), 7.57 (d 1H J=8.8Hz), 8.29 (br d 1H J=7.7Hz), 8.67 (br d 1H J=4.7Hz), 9.14 (s 1H), 13.76 (s 1H)

20 In a similar method according to the Example 1-1 to 1-8 above, the compounds in Example 1-9 to 1-210 were synthesized.

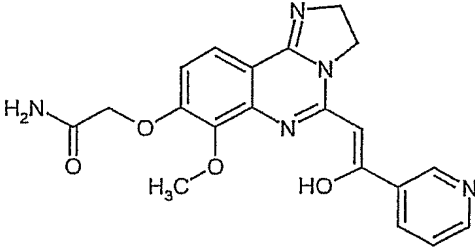
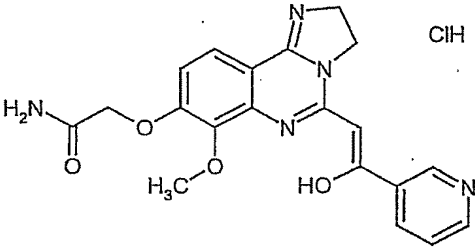
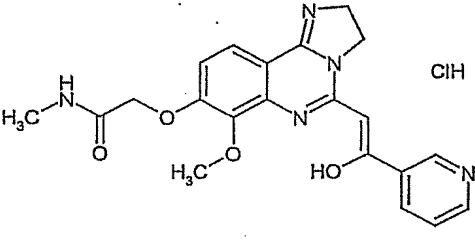
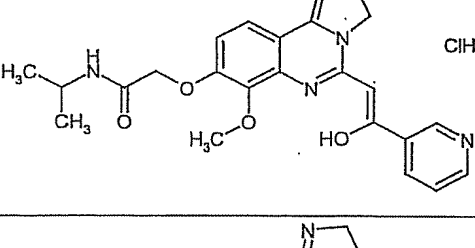
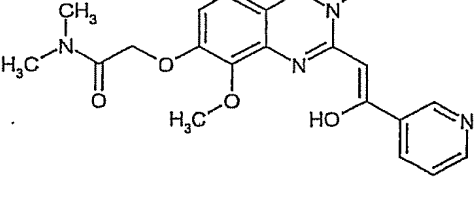
Table 1

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-9		372,81	337	245(dec.)	A
1-10		350,38	351	269-270	A
1-11		386,84	351	249-250	A
1-12		407,43	408	270(dec.)	A

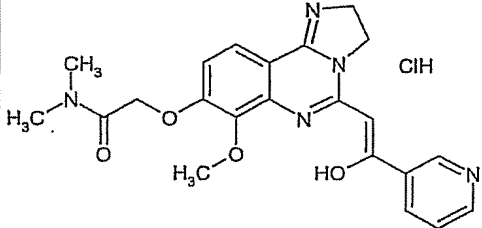
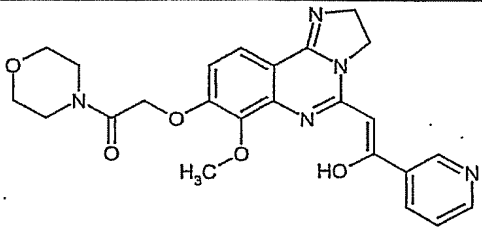
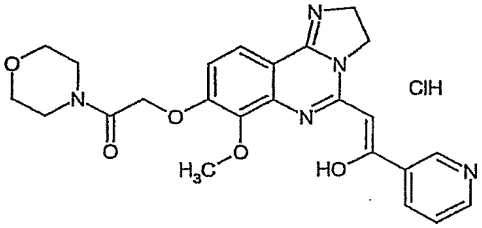
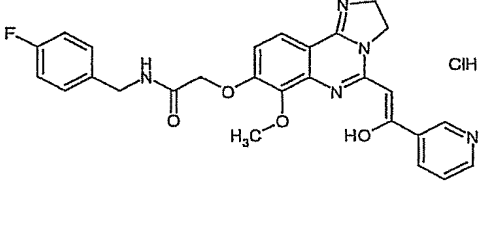
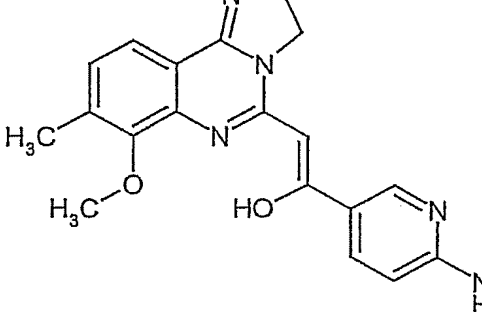
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-13		364,41	365	267-268	A
1-14		378,43	379	252-253	A
1-15		390,45	391	254(dec.)	B
1-16		380,41	381	264-265	A
1-17		416,87	381	215(dec.)	A

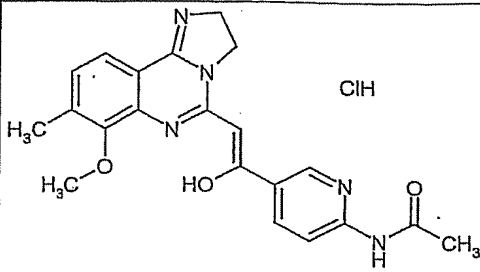
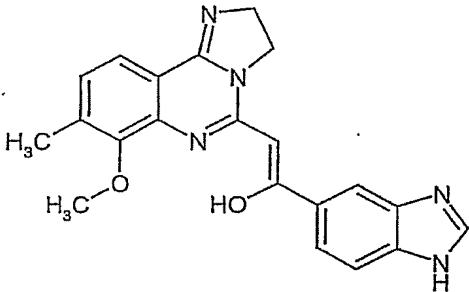
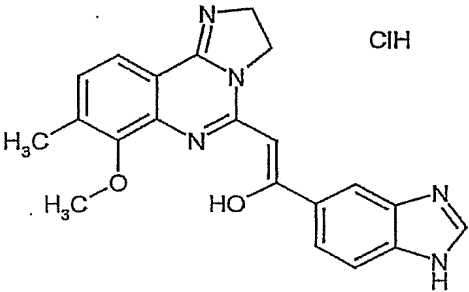
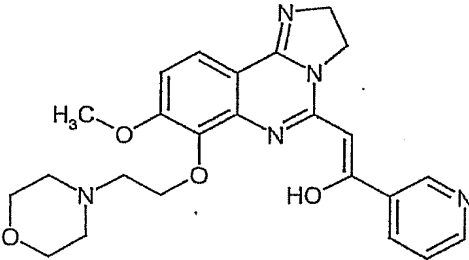
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-18		450,50	451	184-186	B
1-19		407,48	408	183-184	B
1-20		447,54	448	162-163	B
1-21		433,51	434	204-205	A
1-22		430,85	395	240(dec.)	A

- 62 -

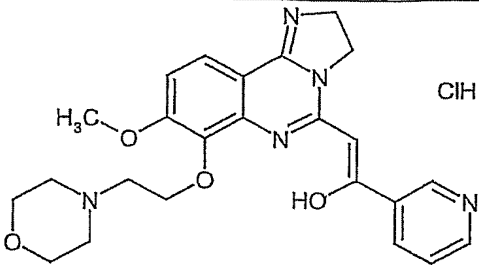
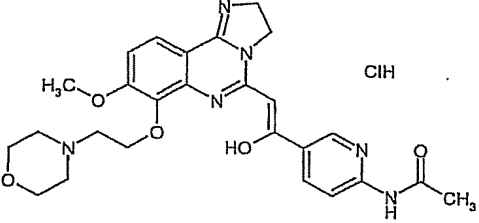
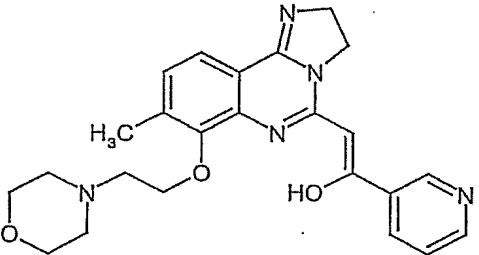
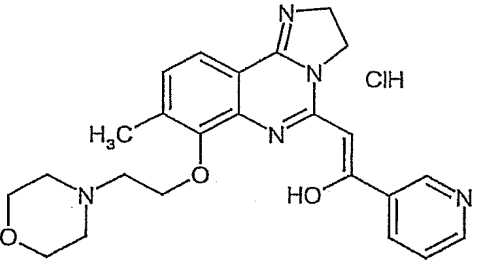
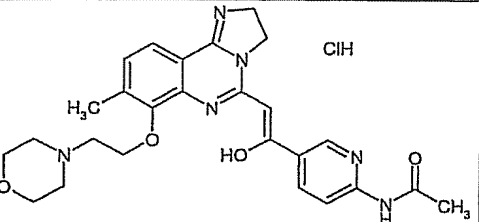
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-23		393,41	394	297-298	A
1-24		429,87	394	235(dec.)	A
1-25		443,89	408	240(dec.)	A
1-26		471,95	436	245(dec.)	A
1-27		421,46	422	241-242	A

- 63 -

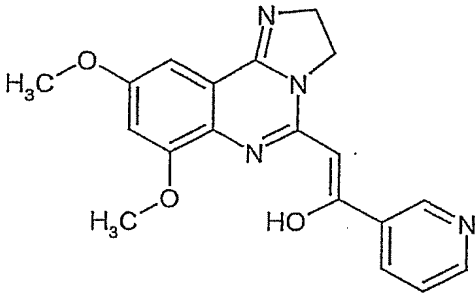
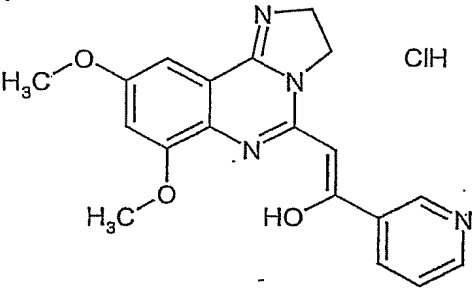
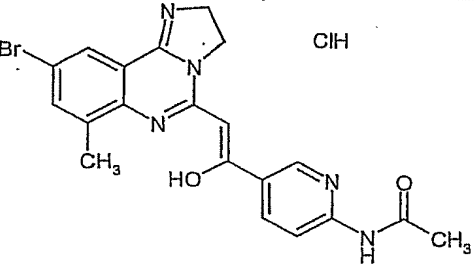
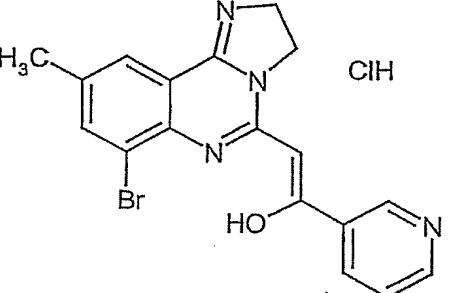
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-28		457,92	422	205(dec.)	A
1-29		463,50	464	234-235	A
1-30		499,96	464	240-241	A
1-31		537,98	502	230-231	B
1-32		391,43	392	>285	A

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-33	 ClH	427,89	392	273	A
1-34		373,42	374	>285	A
1-35	 ClH	409,88	374	270	A
1-36		449,51	450	197	A

- 65 -

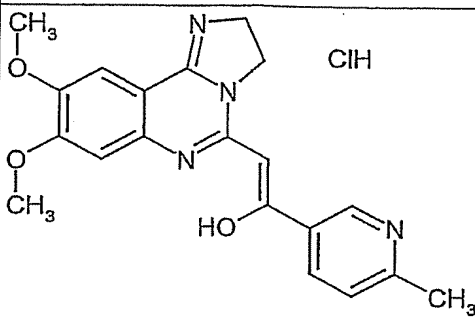
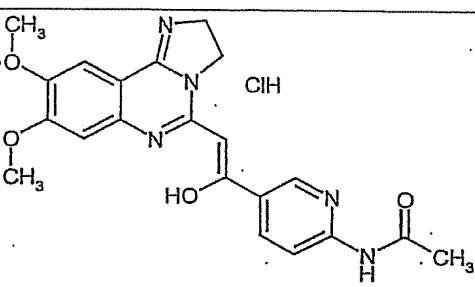
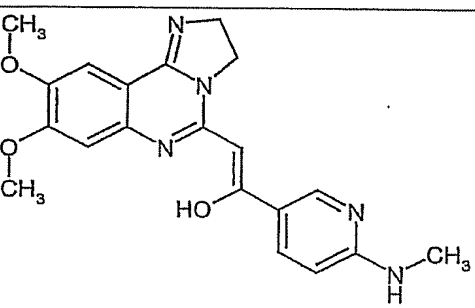
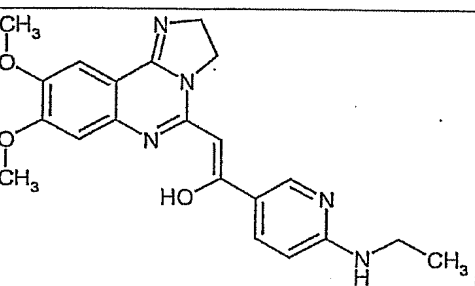
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-37	 ClH	485,97	450	215	A
1-38	 ClH	543,03	507	260	A
1-39		433,51	434	217	B
1-40	 ClH	469,98	434	256(dec.)	B
1-41	 ClH	527,03	491	271	A

- 66 -

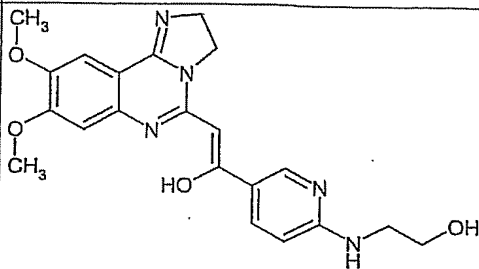
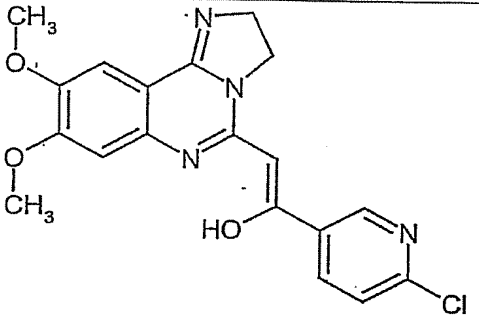
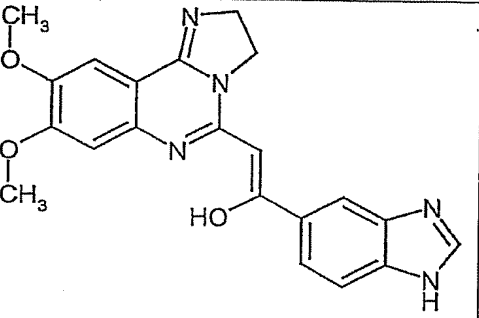
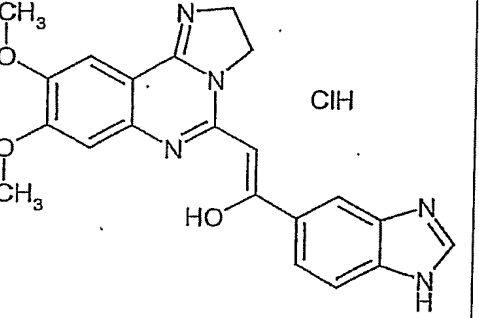
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-42		350,38	351	218	A
1-43		386,84	351	290(dec.)	A
1-44		476,76	442, 440	>290	B
1-45		419,71	385, 383	>290	B

- 67 -

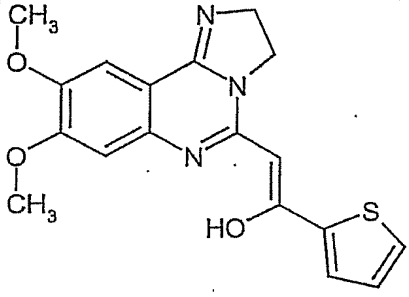
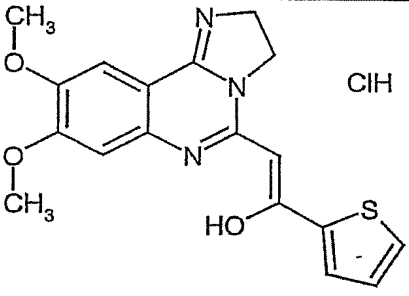
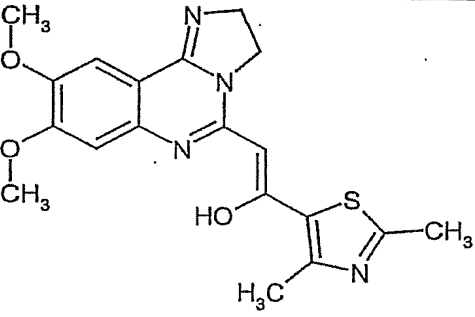
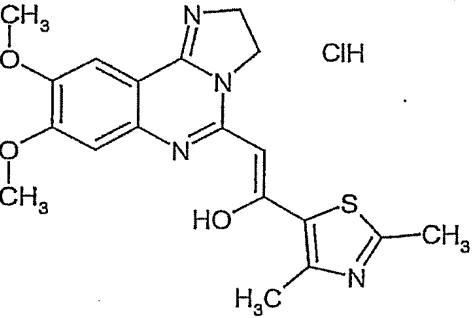
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-46	 ClH	476,76	442, 440	>285	A
1-47	 HO	422,29	424, 422	>285	B
1-48	 ClH	458,75	424, 422	>285	B
1-49	 HO	364,41	365	200-204	A

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-50	 ClH	400,87	365	260(dec.)	B
1-51	 ClH	443,89	408	275-280	B
1-52		379,42	380	321-325	B
1-53		393,45	394	195-198	B

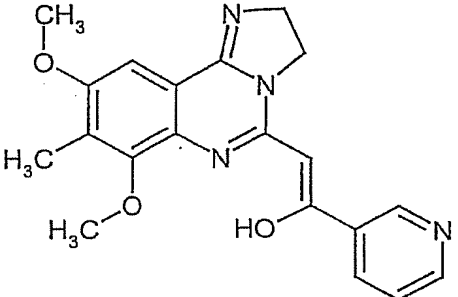
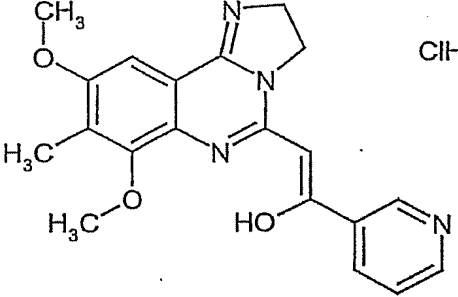
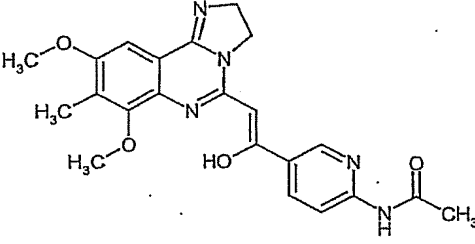
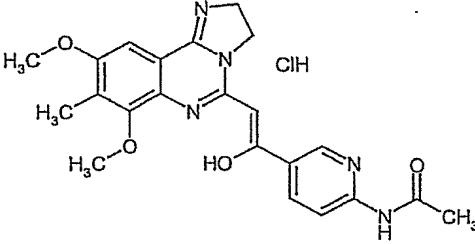
- 69 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-54		409,45	410	207	B
1-55		384,83	385	283	B
1-56		389,42	390	212-215	A
1-57		425,88	390	240(dec.)	A

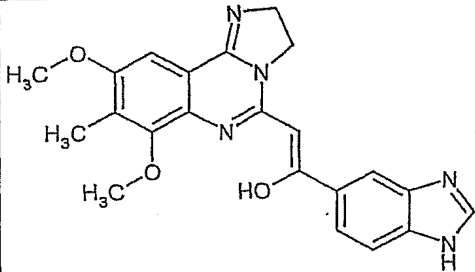
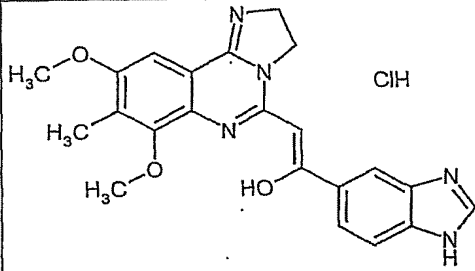
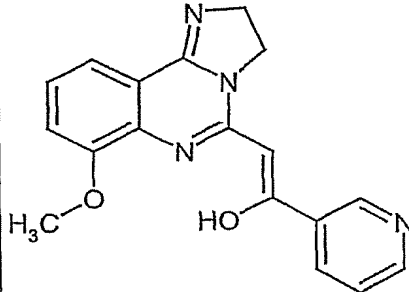
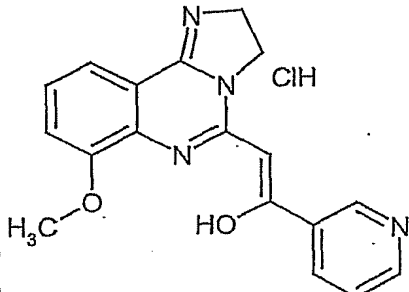
- 70 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-58		355,42	356	250	B
1-59		391,88	356	266-268	B
1-60		384,46	385	292	A
1-61		420,92	385	268-271	A

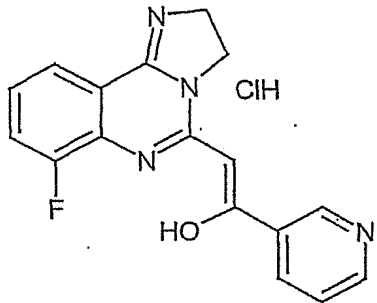
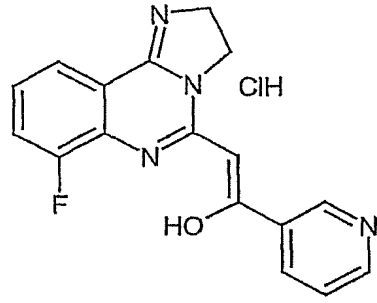
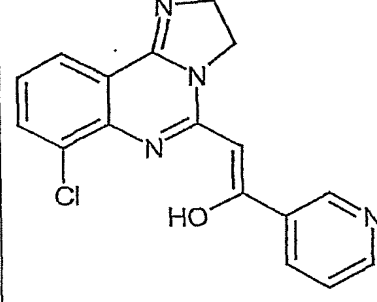
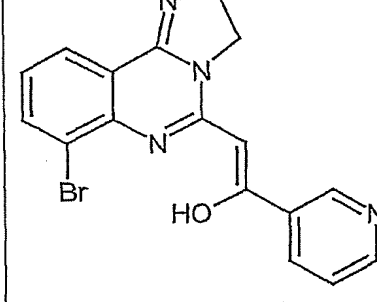
- 71 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-62		364,41	365	278	A
1-63		400,87	365	285	A
1-64		421,46	422	>285	A
1-65		457,92	422	>285	A

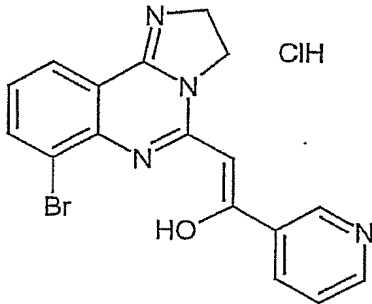
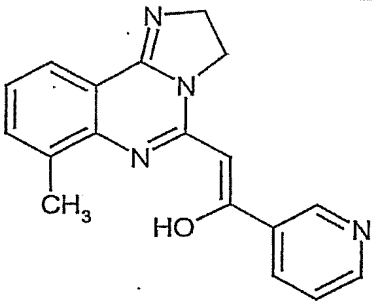
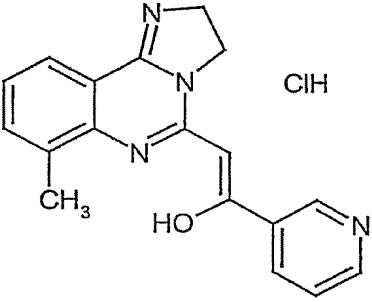
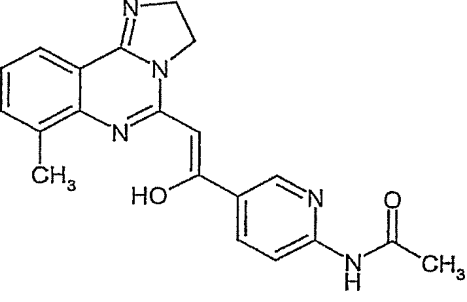
- 72 -

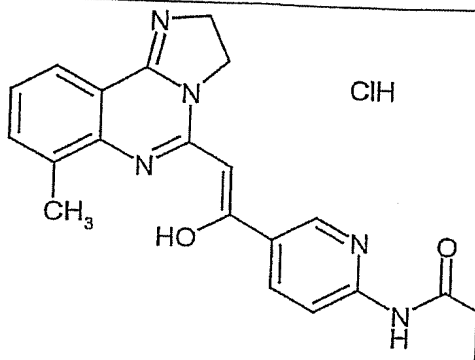
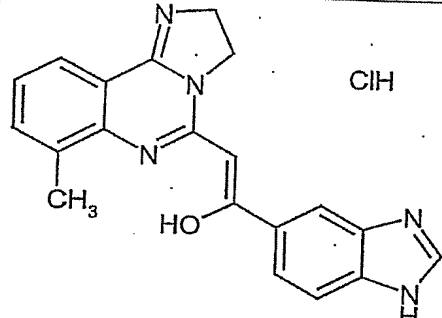
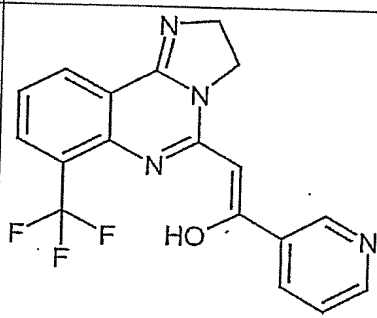
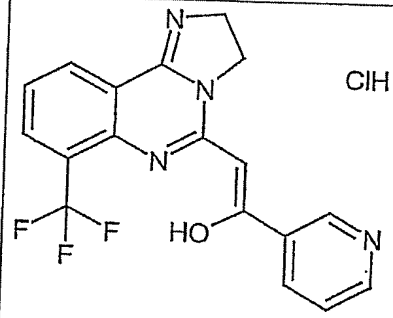
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-66		403,44	404	280	B
1-67		439,91	404	>285	B
1-68		320,35	321	275	A
1-69		356,81	321	285	A

- 73 -

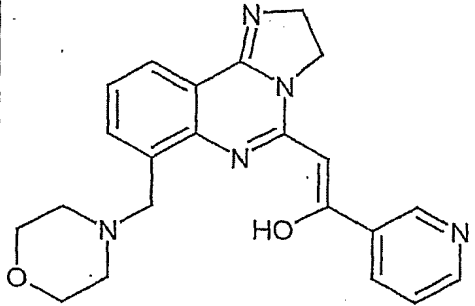
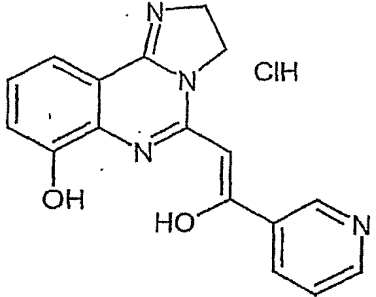
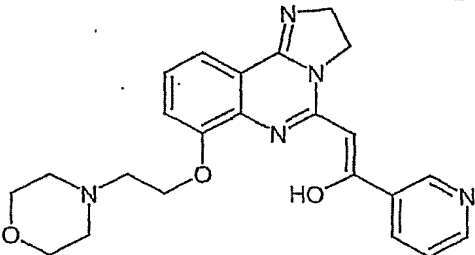
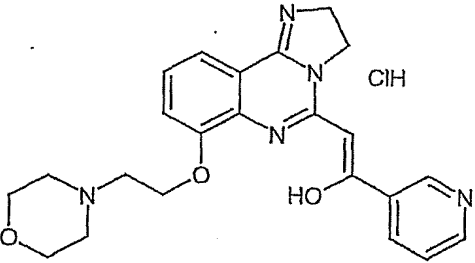
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-70		308,32	309	218	A
1-71		344,78	309	303	B
1-72		324,77	325	210(dec.)	B
1-73		369,22	371, 369	120(dec.)	B

- 74 -

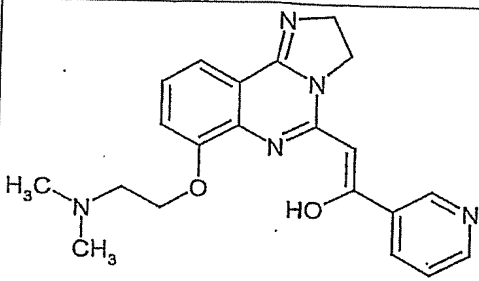
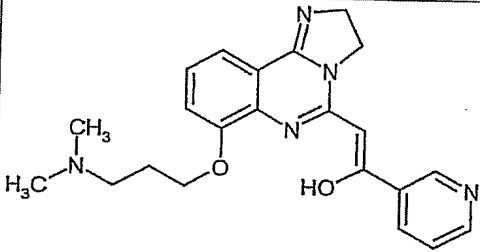
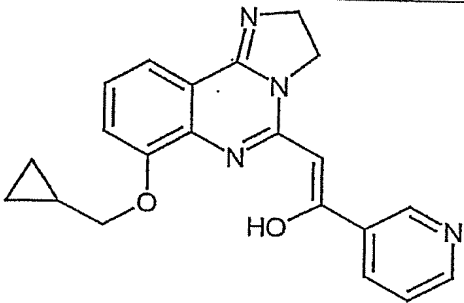
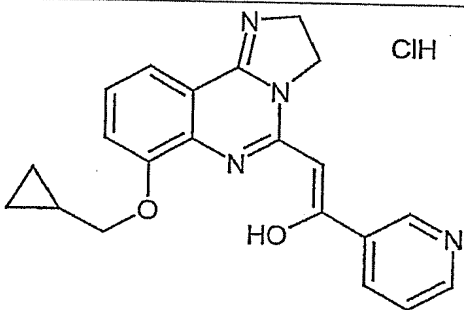
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-74	 ClH	405,68	371, 369	246	B
1-75		304,35	305	248	B
1-76	 ClH	340,82	305	>290	B
1-77		361,41	362	>285	A

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-78	 ClH	397,87	362	>285	A
1-79	 ClH	379,85	344	>285	A
1-80		358,33	359	275	B
1-81	 ClH	394,79	359	>290	B

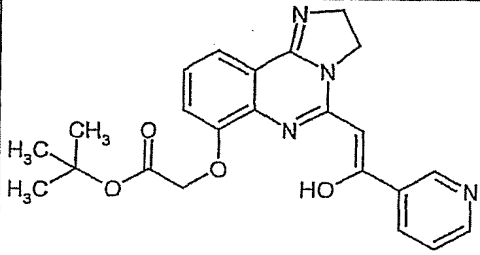
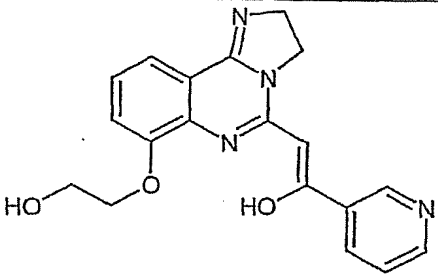
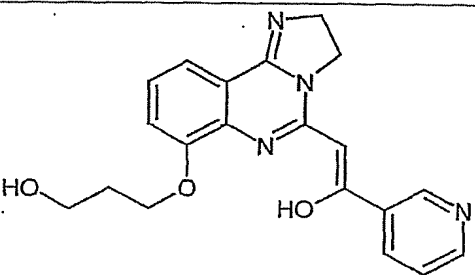
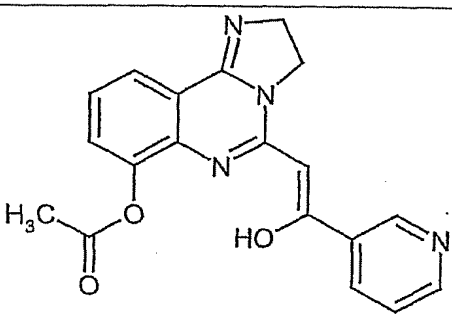
- 76 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-82		389,46	390	198 - 202 (dec.)	B
1-83		342,79	307	>250	B
1-84		419,49	420	195-196	B
1-85		455,95	420	261-262	B

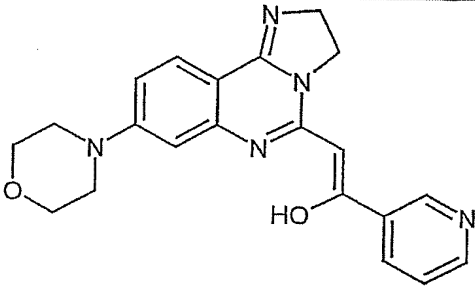
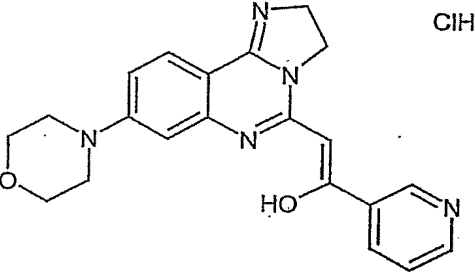
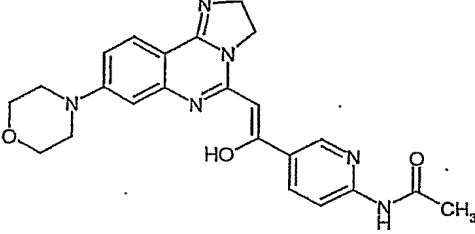
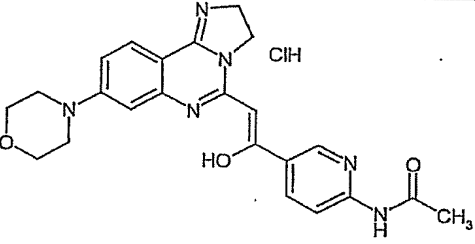
- 77 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-86		377,45	378	186-187	B
1-87		391,48	392	235(dec.)	B
1-88		360,42	361	203(dec.)	B
1-89		396,88	361	>300	B

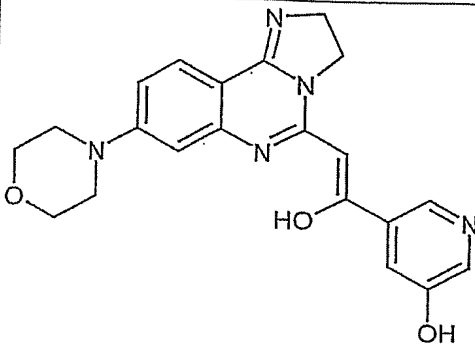
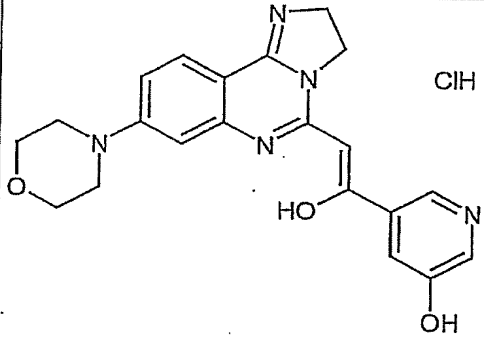
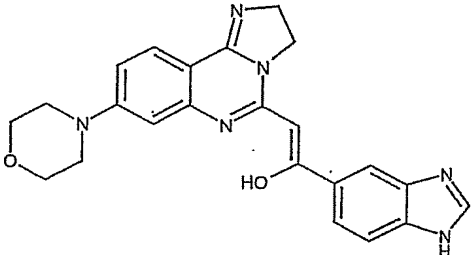
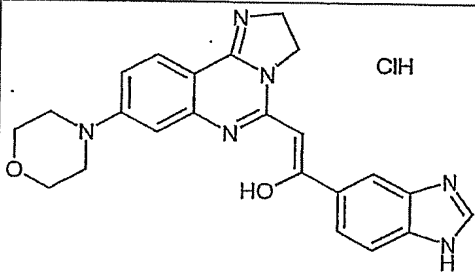
- 78 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-90		420,47	421	222-223	A
1-91		350,38	351	211-212	B
1-92		364,41	365	203-205	A
1-93		348,36	349	225-226	B

- 79 -

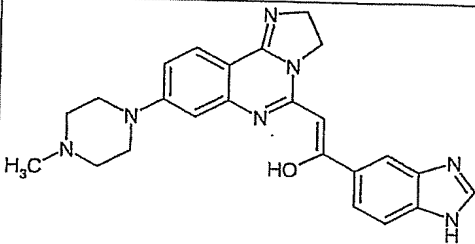
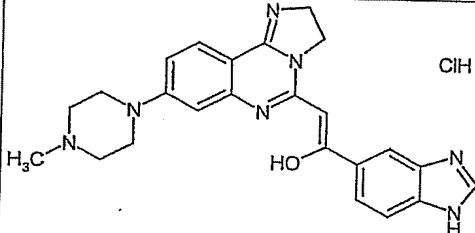
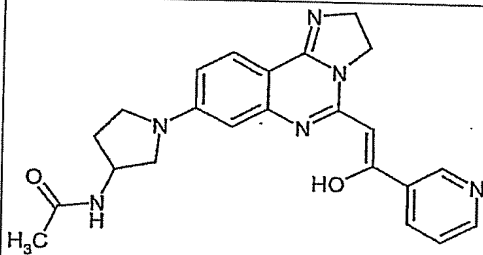
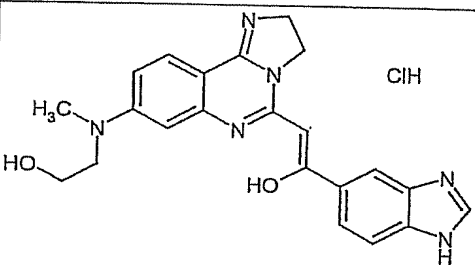
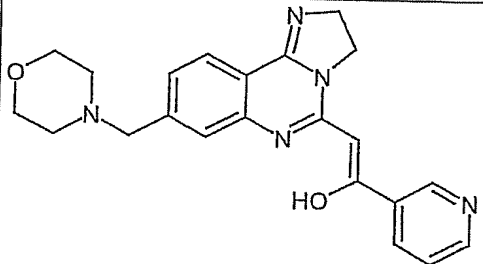
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-94		375,43	376	282	B
1-95	 ClH	411,89	376	>300	B
1-96		432,49	433	269(dec.)	A
1-97	 ClH	468,95	433	246	A

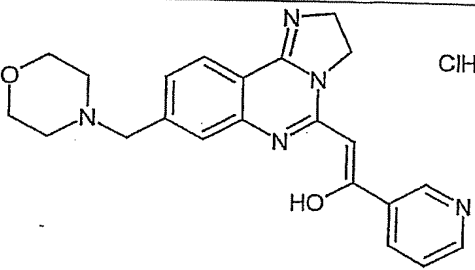
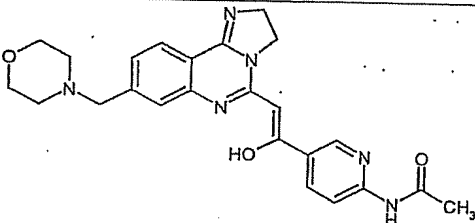
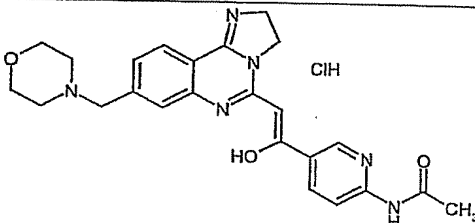
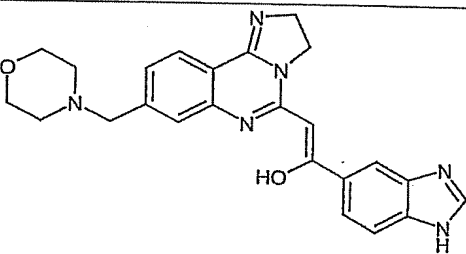
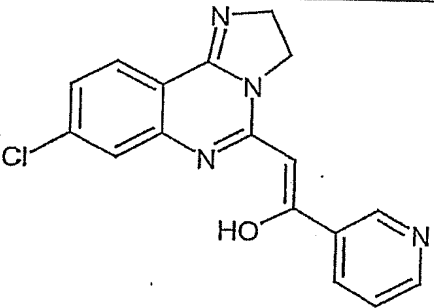
- 80 -

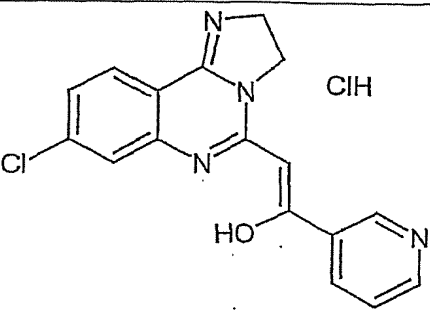
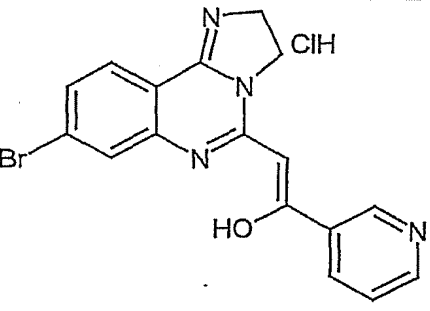
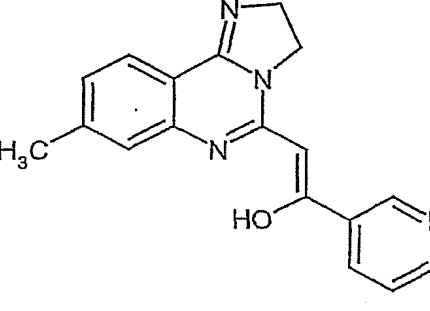
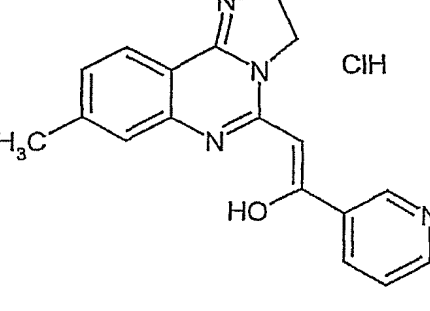
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-98		391,43	392	337(dec.)	A
1-99	 ClH	427,89	392	312(dec.)	A
1-100		414,47	415	232	A
1-101	 ClH	450,93	415	286(dec.)	A

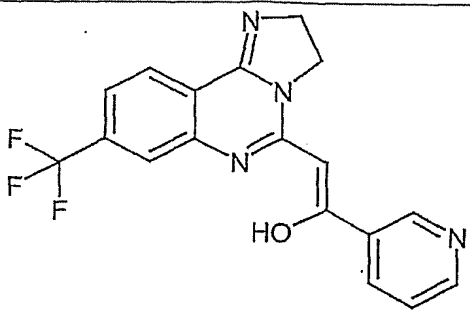
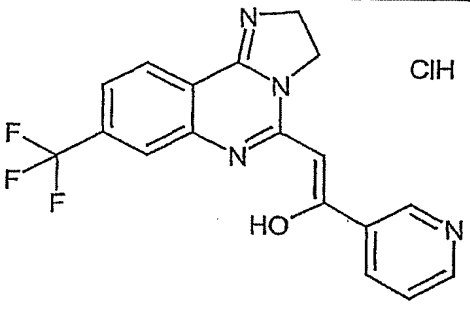
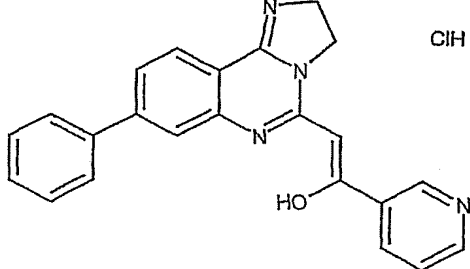
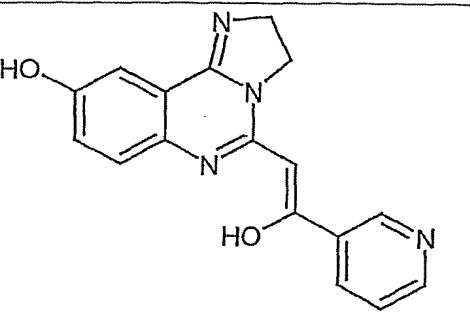
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-102	 <chem>CC(=O)Nc1ccc(cc1)/C=C(O)c2nc3c(ncn3c2)C4=CC=C(C=C4)N5CCOCC5</chem> ClH	482,97	447	238(dec.)	B
1-103	 <chem>Oc1ccc(cc1)/C=C(O)c2nc3c(ncn3c2)C4=CC=C(C=C4)N5CCN(CCN5Cc6ccccc6)</chem> ClH	501,04	466	257	B
1-104	 <chem>Oc1ccc(cc1)/C=C(O)c2nc3c(ncn3c2)C4=CC=C(C=C4)N5CCN(CCN5C)</chem> ClH	424,94	389	288	B
1-105	 <chem>CC(=O)Nc1ccc(cc1)/C=C(O)c2nc3c(ncn3c2)C4=CC=C(C=C4)N5CCN(CCN5C)</chem>	445,53	446	292(dec.)	B
1-106	 <chem>CC(=O)Nc1ccc(cc1)/C=C(O)c2nc3c(ncn3c2)C4=CC=C(C=C4)N5CCN(CCN5C)</chem> ClH	481,99	446	280(dec.)	B

- 82 -

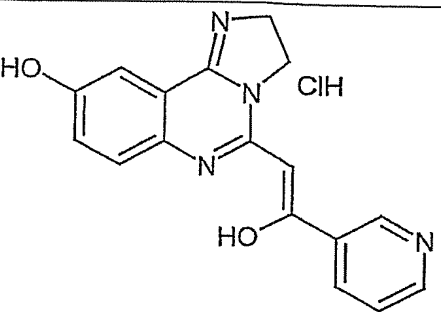
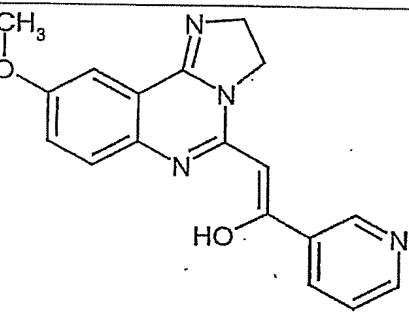
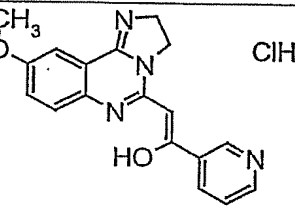
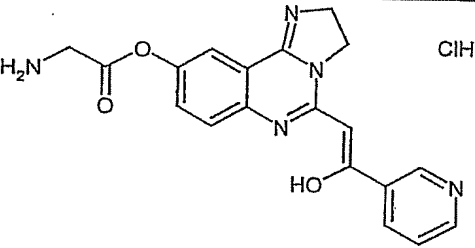
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-107		427,51	428	207	A
1-108		463,97	428	>300	B
1-109		416,49	416		A
1-110		438,92	403	231(dec.)	B
1-111		389,46	390	204	B

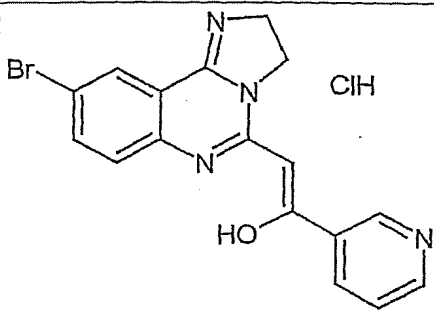
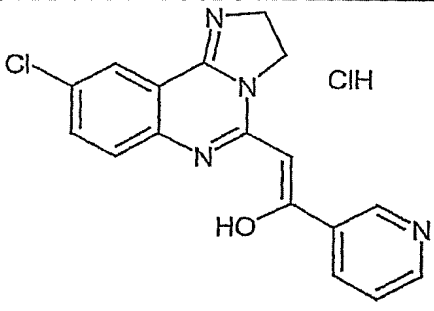
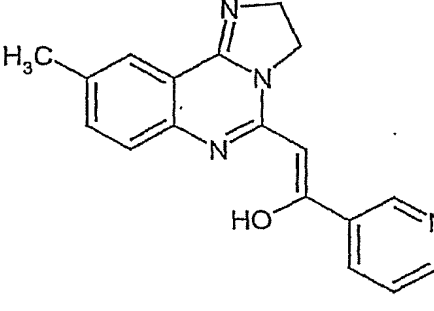
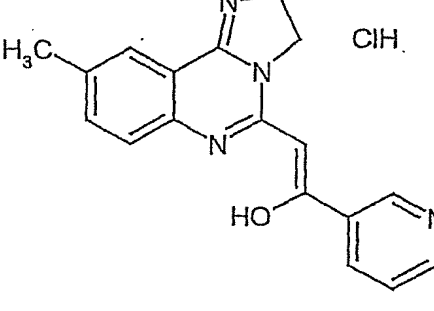
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-112	 ClH	425,92	390	242	B
1-113		446,51	447	245	B
1-114	 ClH	482,97	447	260	B
1-115		428,50	429	219	B
1-116		324,77	325	226	B

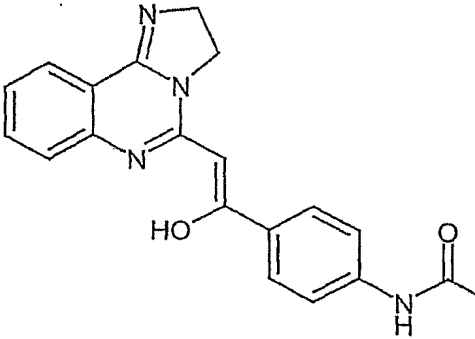
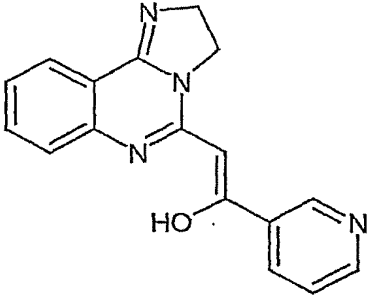
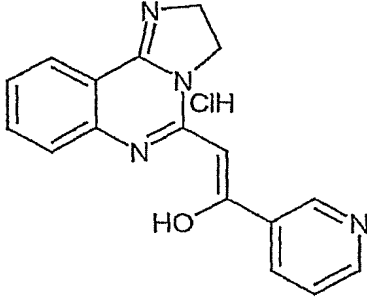
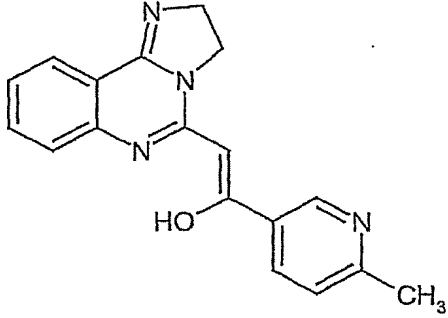
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-117	 ClH	361,23	326	280(dec.)	B
1-118	 ClH	405,68	371, 369	233	B
1-119	 H ₃ C	304,35	305	224	B
1-120	 ClH	340,82	305	>330	B

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-121		358,33	359	264	C
1-122	 ClH	394,79	359	321	B
1-123	 ClH	402,89	367	>300	B
1-124		306,33	307	302-303	B

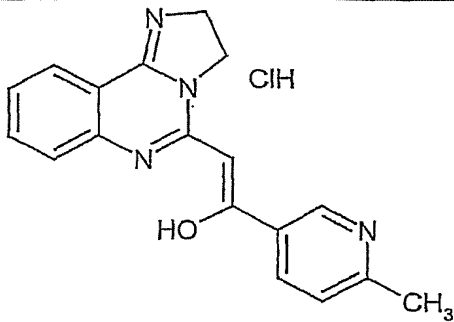
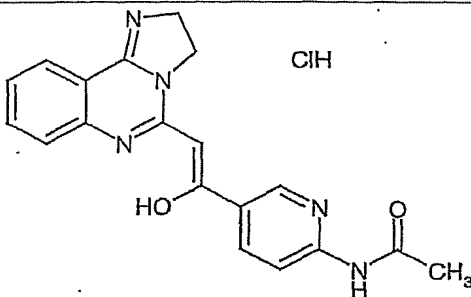
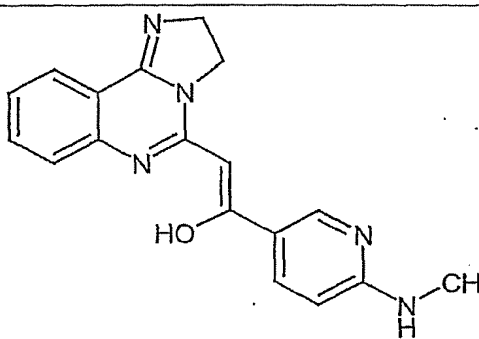
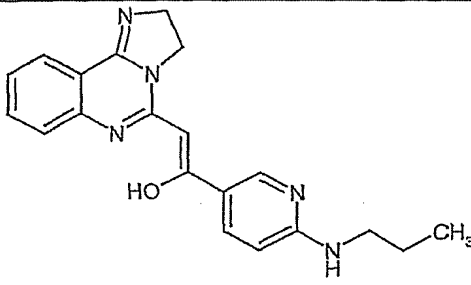
- 86 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-125	 <chem>Oc1ccc2nc3c(ncn3COC(=O)c4cccnc4)c2cc1.Cl</chem>	342,79	307	>300	A
1-126	 <chem>COc1ccc2nc3c(ncn3COC(=O)c4cccnc4)c2cc1.Cl</chem>	320,35	321	199	B
1-127	 <chem>COc1ccc2nc3c(ncn3COC(=O)c4cccnc4)c2cc1.Cl</chem>	356,81	321	>300	B
1-128	 <chem>NCCOC(=O)c1ccc2nc3c(ncn3COC(=O)c4cccnc4)c2cc1.Cl</chem>	399,84	364	>300	A

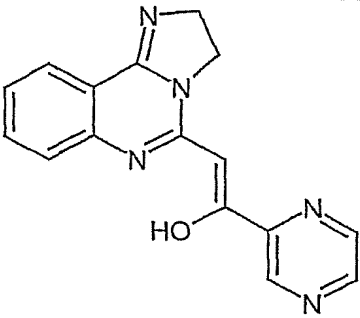
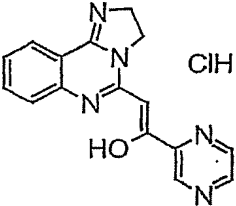
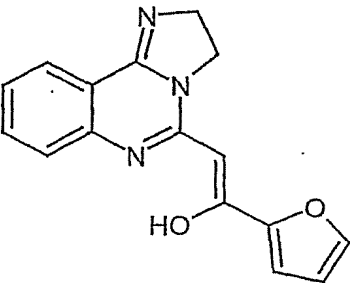
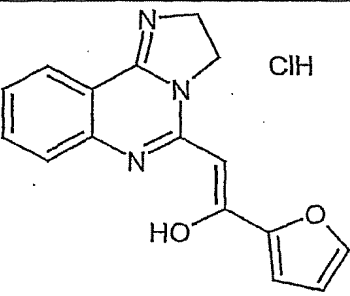
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-129	 ClH	405,68	371, 369	>330	B
1-130	 ClH	361,23	326	>330	B
1-131		304,35	305	212	B
1-132	 ClH	340,82	305	>290	B

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-133		346,39	347	>300	B
1-134		290,33	291	202	B
1-135		326,79	291	260(dec.)	B
1-136		304,35	305	217-219	B

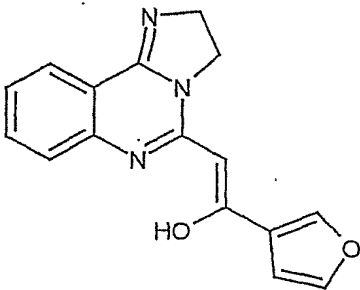
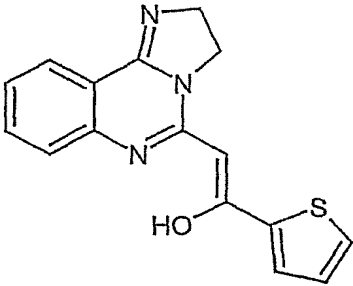
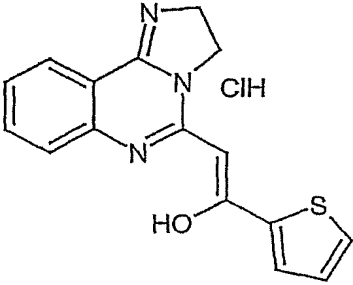
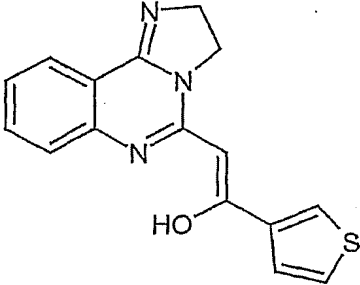
- 89 -

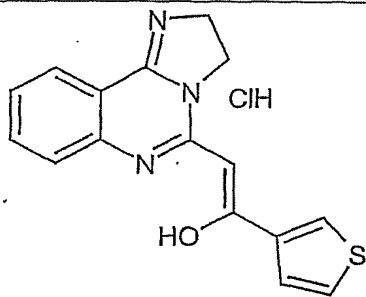
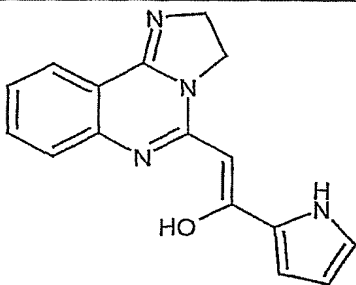
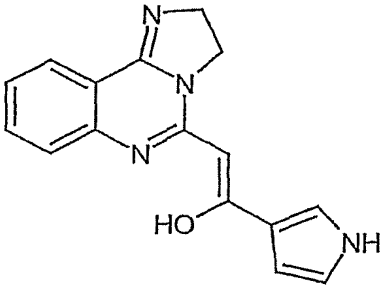
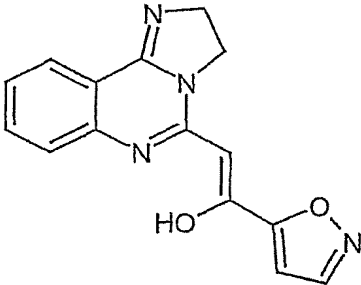
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-137	 ClH	340,82	305	>300	B
1-138	 ClH	383,84	348	327	A
1-139		319,37	320	232-237	A
1-140		347,42	348	197	B

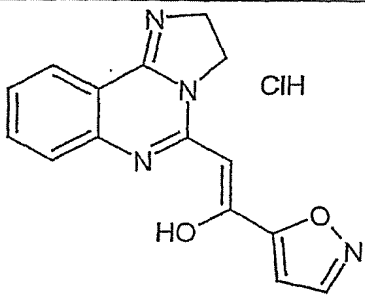
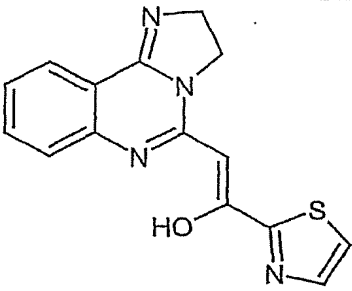
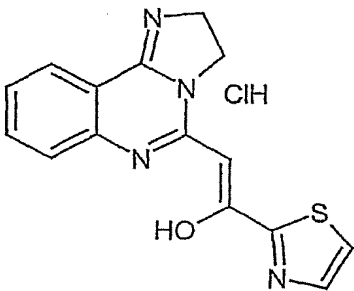
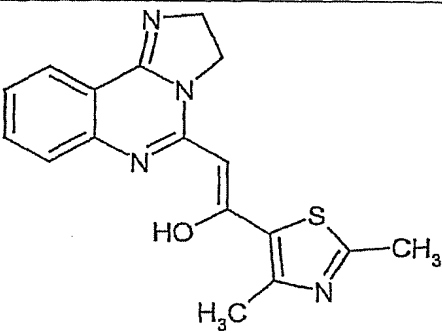
- 90 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-141	 <chem>C1=CN2C(=C1)N=CN=C2C=Cc3ccncc3</chem>	291,31	292	233-235	B
1-142	 <chem>C1=CN2C(=C1)N=CN=C2C=Cc3ccncc3.Cl</chem>	327,78	292	217-222	B
1-143	 <chem>C1=CN2C(=C1)N=CN=C2C=Cc3ccoc3</chem>	279,30	280	192	B
1-144	 <chem>C1=CN2C(=C1)N=CN=C2C=Cc3ccoc3.Cl</chem>	315,76	280	>300	B

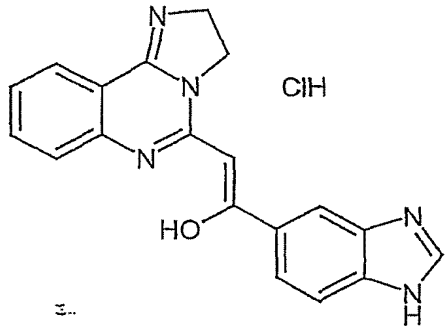
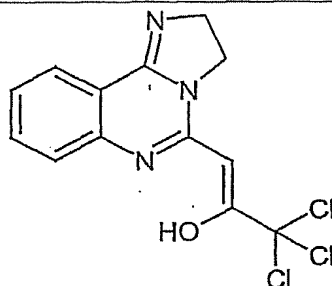
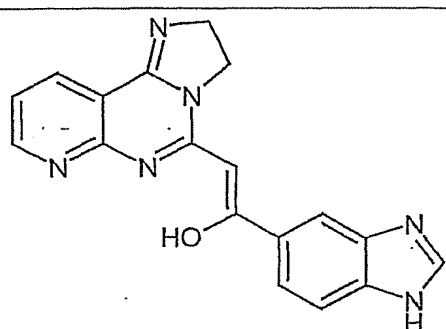
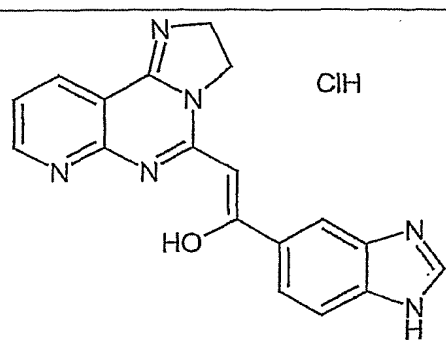
- 91 -

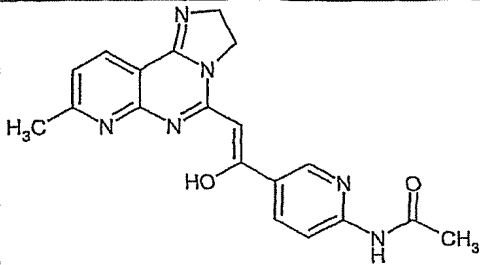
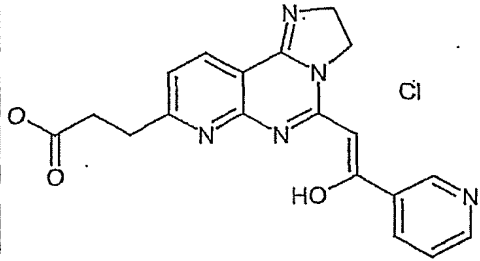
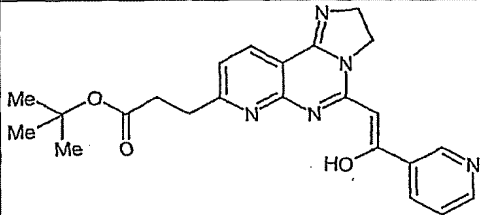
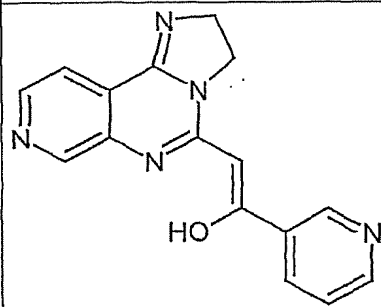
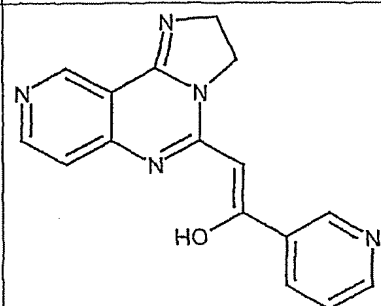
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-145		279,30	280	155-156	B
1-146		295,37	296	193	A
1-147		331,83	296	>300	A
1-148		295,37	296	182-183	B

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-149		331,83	296	>300	A
1-150		278,32	279	247	B
1-151		278,32	279	247-249	A
1-152		280,29	281	148	B

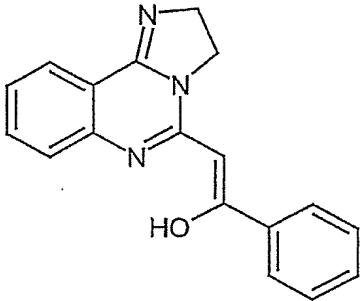
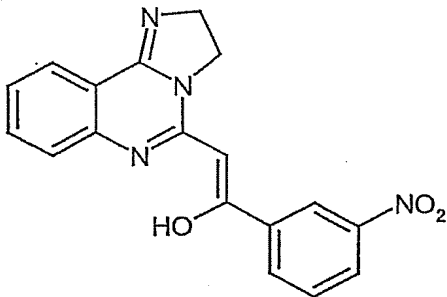
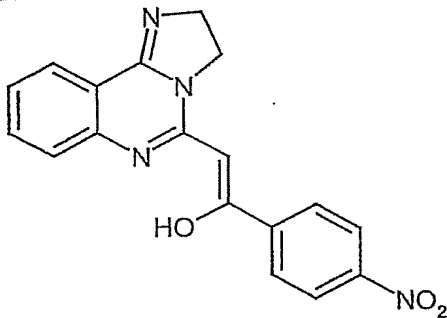
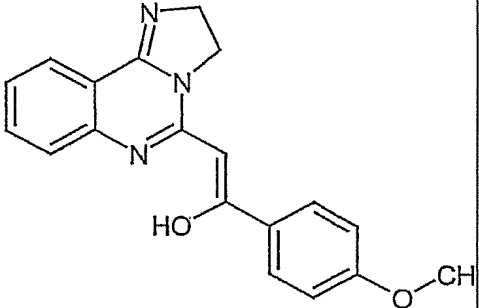
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-153	 ClH	316,75	281	245(dec.)	B
1-154		296,35	297	208-210	A
1-155	 ClH	332,81	297	> 300	B
1-156		324,41	325	222	A

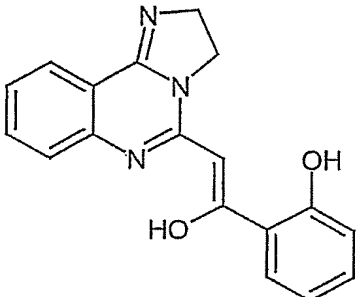
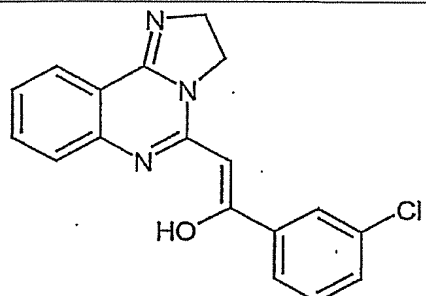
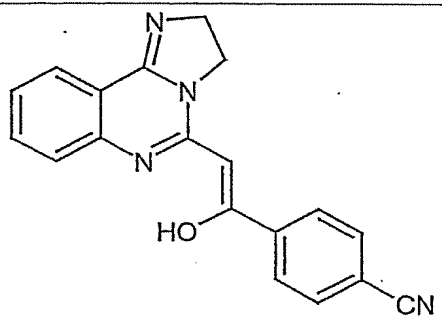
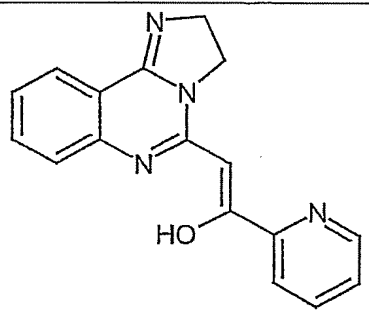
- 94 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-157	 ClH	365,83	330	>300	B
1-158		330,60	330	190(dec.)	B
1-159		330,35	331	>300	A
1-160	 ClH	366,81	331	247(dec.)	B

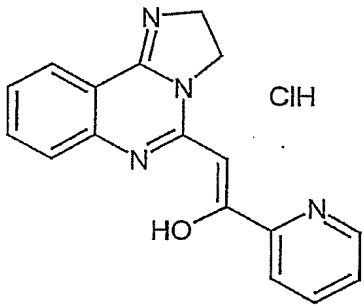
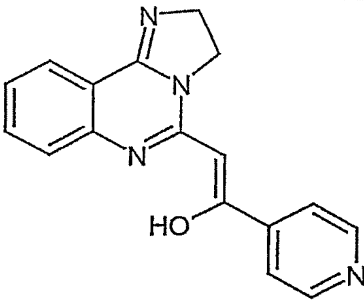
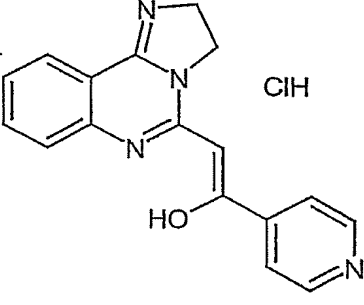
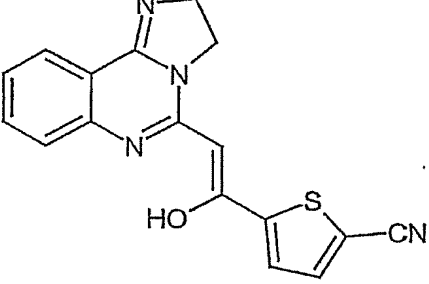
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-161		362,39	363	>300	B
1-162		399,84	400	>300	B
1-163		419,49	420	200	B
1-164		291,31	292	230	B
1-165		291,31	292	250	B

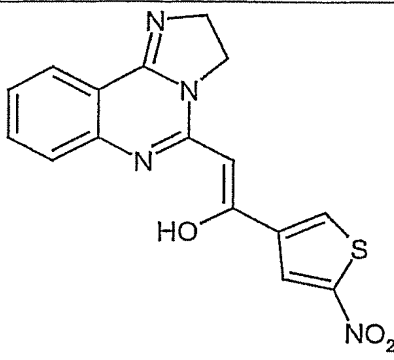
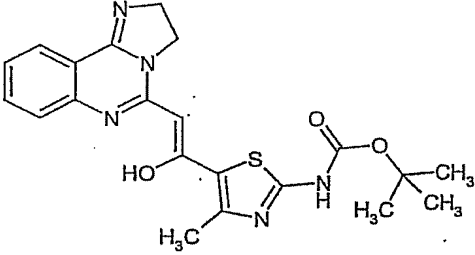
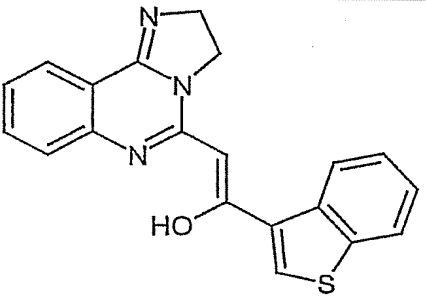
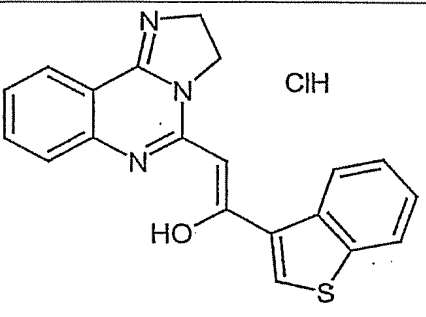
- 96 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-166		289,34	290	130-139	C
1-167		334,34	335	276	D
1-168		334,34	335	240-248	D
1-169		319,37	320	212-214	D

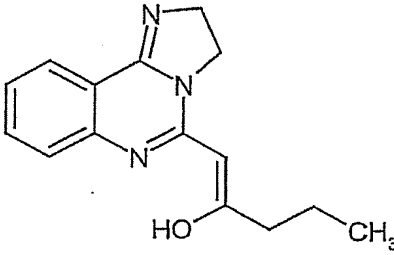
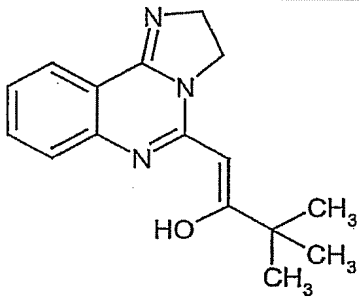
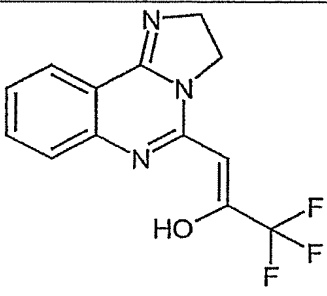
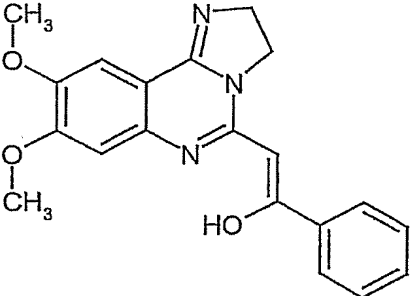
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-170		305,34	306	252-256	D
1-171		323,78	324	224-227	D
1-172		314,35	315	260-264	D
1-173		290,33	291	195	C

- 98 -

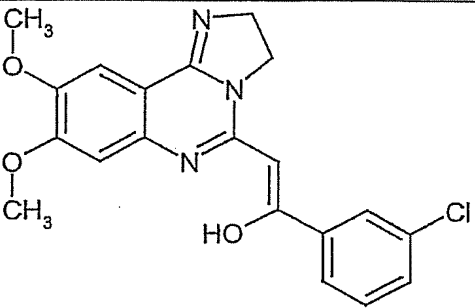
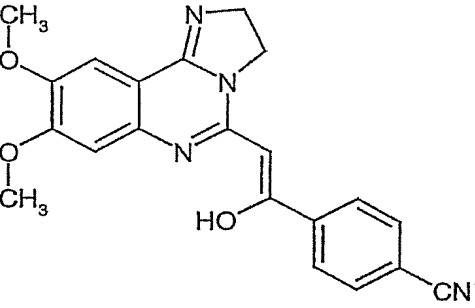
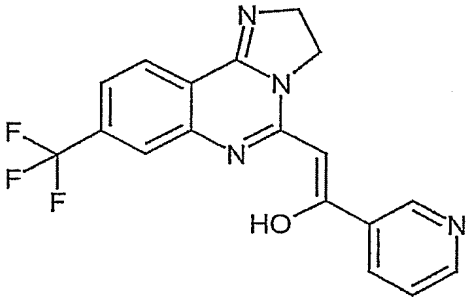
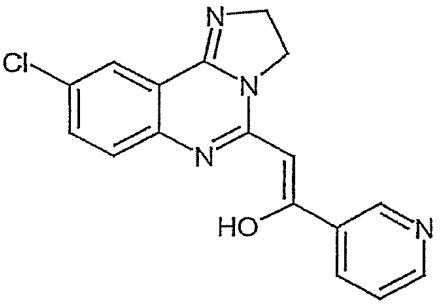
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-174	 ClH	326,79	291	235-240	C
1-175		290,33	291	204-205	B
1-176	 ClH	326,79	291	235(dec.)	B
1-177		320,38	321	256	C

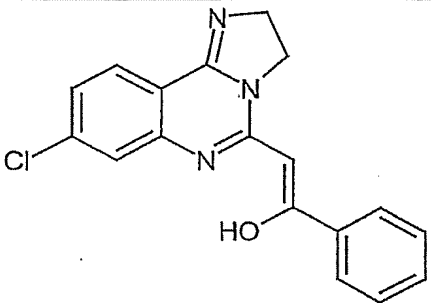
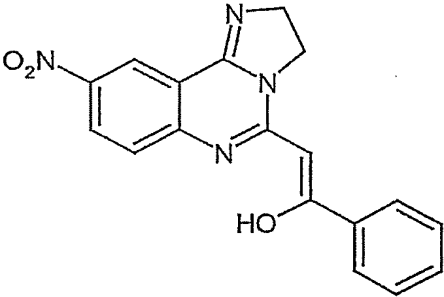
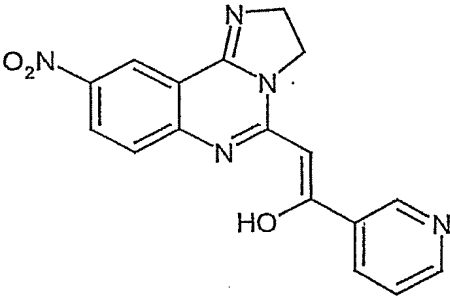
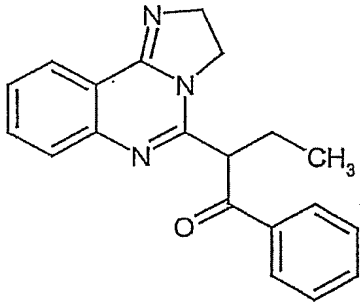
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-178		340,36	341	255-258	D
1-179		425,51	426	>300	D
1-180		345,43	346	220-225	D
1-181	 ClH	381,89	346	>300	D

- 100 -

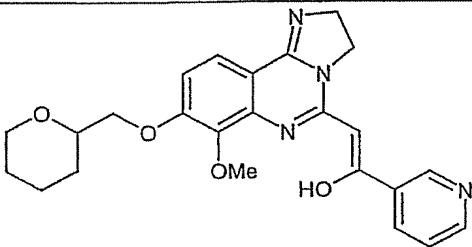
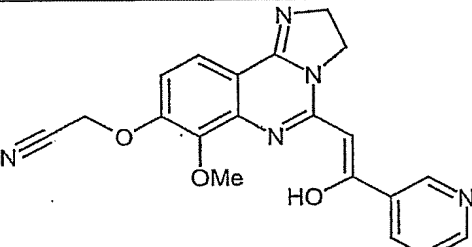
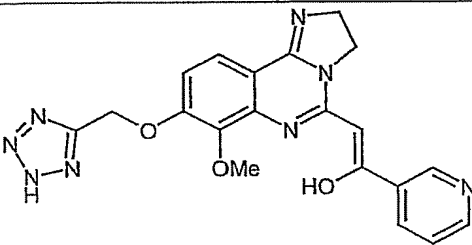
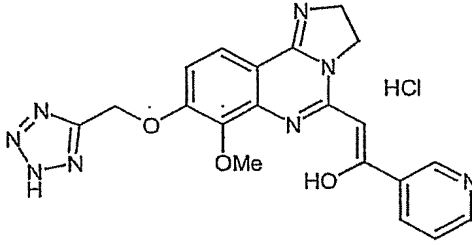
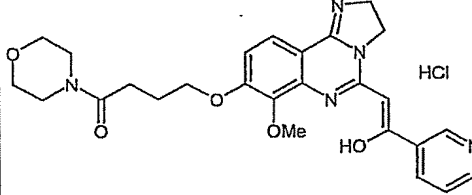
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-182		255,32	256	113	D
1-183		269,35	270	134-138	C
1-184		281,24	282	240	C
1-185		349,39	350	249-252	C

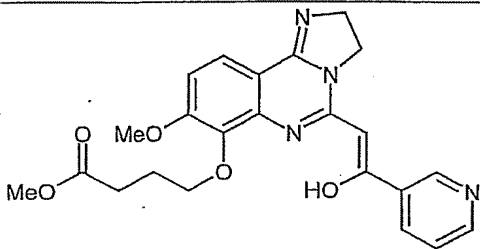
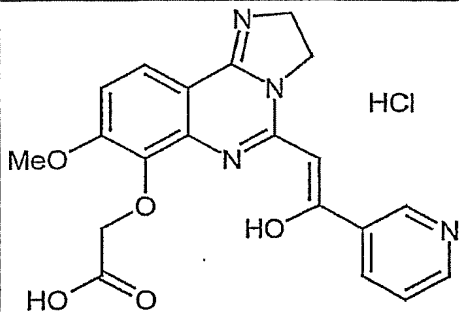
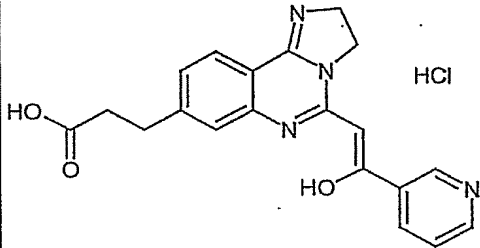
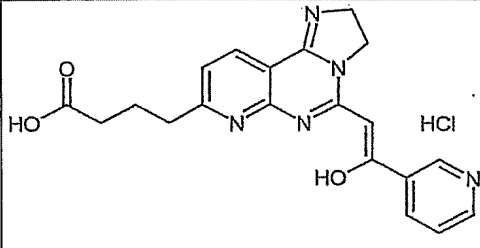
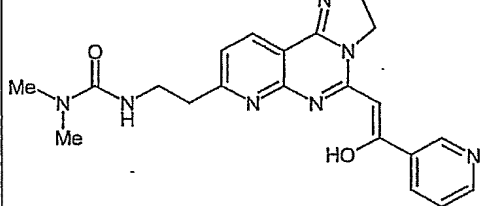
- 101 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-186		383,84	384	257-259	D
1-187		374,40	375	307-308	D
1-188		358,33	359	264	C
1-189		324,77	325	260	C

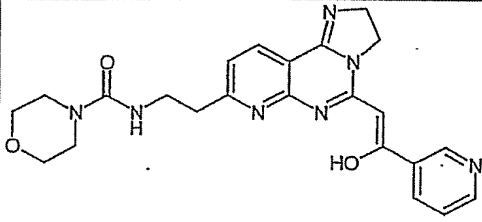
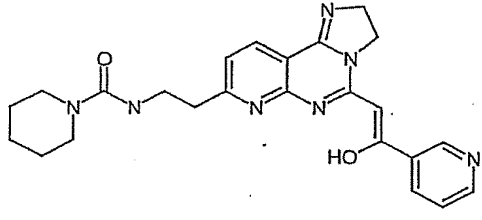
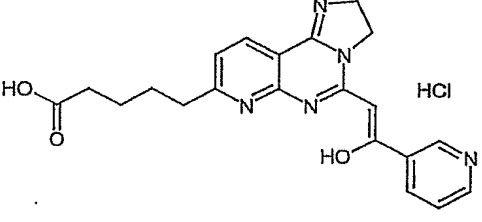
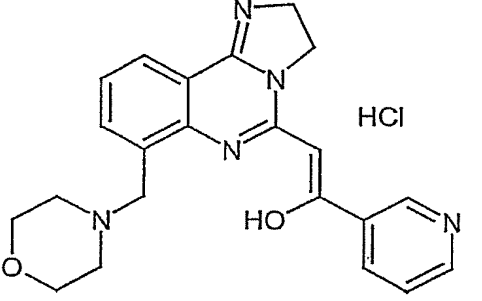
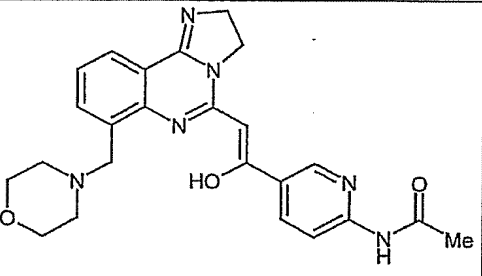
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-190		323,78	324	186-188	C
1-191		334,34	335	259-262	D
1-192		335,32	336	306	C
1-193		317,39	318	156-160	D

- 103 -

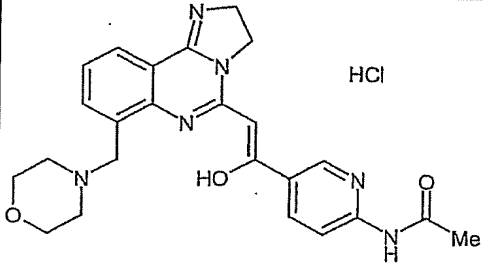
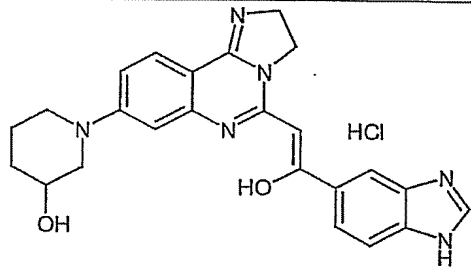
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-194		434,50	435	233-234	A
1-195		375,39	376	284-285	A
1-196		418,42	419	229-231	A
1-197		454,88	419	217-218	A
1-198		528,01	492	215-216	A

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-199		436,47	437	178-179	A
1-200		430,85	395	286(dec.)	B
1-201		398,85	363	273(dec.)	A
1-202		413,87	378	285(dec.)	B
1-203		405,46	406	228	B

- 105 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-204		447,50	448	262	C
1-205		445,53	446	246	B
1-206		427,89	392	267	A
1-207		425,92	390	259(dec.)	B
1-208		446,51	447	253(dec.)	B

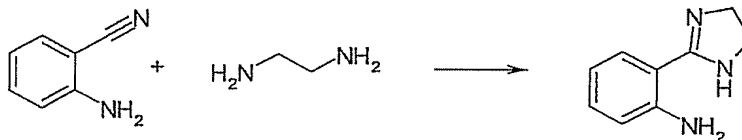
- 106 -

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-209	 HCl	482,97	447	>260	B
1-210	 HCl	464,96	429	>300	A

Example 2-1:

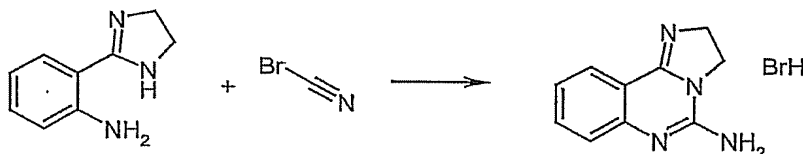
N-(2,3-Dihydroimidazo[1,2-*c*]quinazolin-5-yl)nicotinamide

(1) 2-(4,5-Dihydro-1*H*-imidazol-2-yl)aniline



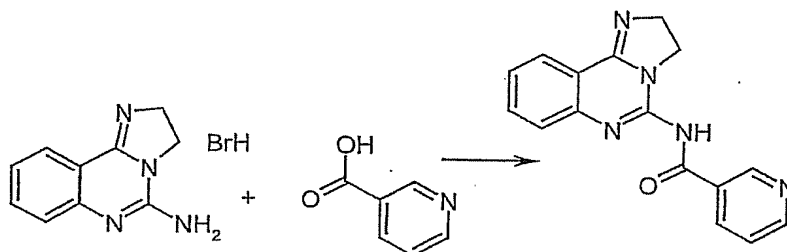
2-Aminobenzonitrile (9.00 g, 76.2 mmol) was added at 0°C to ethylenediamine (25.5 ml, 381 mmol) in small portions with stirring. After phosphorus pentasulfide (200 mg, 0.900 mmol) was added, the mixture was stirred at 100°C overnight. After cooling to 0°C, the reaction was diluted with water. The resulting white precipitate was collected by filtration, washed with water and diethyl ether, and dried under reduced pressure to give 2-(4,5-dihydro-1*H*-imidazol-2-yl)aniline (10.0 g, 81% yield).

(2) 2,3-Dihydroimidazo[1,2-*c*]quinazolin-5-ylamine hydrobromide



To a suspension of 2-(4,5-dihydro-1*H*-imidazol-2-yl)aniline (5.00 g, 31.0 mmol) in 85% methanol (60 ml) at 0°C was added cyanogen bromide (3.61 g, 34.1 mmol) by portions. This mixture was stirred at room temperature overnight. After the mixture was concentrated under reduced pressure, the resulting precipitate was collected by filtration. This pale green solid was washed with water, methanol and diethyl ether successively, and dried under reduced pressure to give 2,3-dihydroimidazo[1,2-*c*]quinazolin-5-ylamine hydrobromide (4.94 g, 60% yield).

- 108 -

(3) *N*-(2,3-Dihydroimidazo[1,2-*c*]quinazolin-5-yl)nicotinamide

To a suspension of 2,3-dihydroimidazo[1,2-*c*]quinazolin-5-ylamine hydrobromide (500 mg, 1.87 mmol) and nicotinic acid (346 mg, 2.81 mmol) in *N,N*-dimethylformamide (25 ml) at room temperature was added benzotriazole-1-yl-oxy-trispyrrolidino-phosphonium hexafluorophosphate (1.46 g, 2.81 mmol) followed by *N,N*-diisopropylethylamine (1.30 ml, 7.49 mmol). The mixture was heated at 80°C for 4 hours. After cooling to room temperature, the mixture was quenched with aqueous saturated NaHCO₃ solution. The resulting precipitate was collected by filtration, washed with water and diethyl ether, and dried under reduced pressure to give *N*-(2,3-dihydroimidazo[1,2-*c*]quinazolin-5-yl)nicotinamide (450 mg, 83% yield).

Melting point: 238-239°C (decomposition)

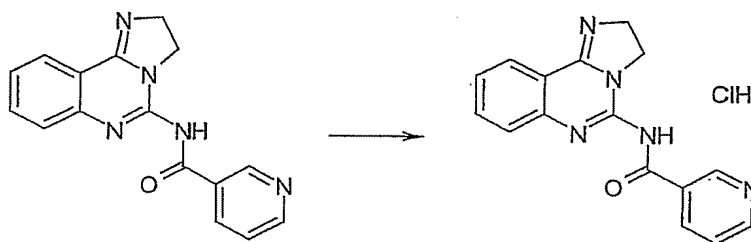
Mass spectrometry: 292

In vitro PI3K-β inhibitory activity: B

In vitro PI3K-γ inhibitory activity: A

¹H-NMR (300 MHz, DMSO-*d*₆): δ 4.00 - 4.11 (2H, m), 4.11 - 4.21 (2H, m), 7.29 (1H, ddd, *J* = 3.0, 5.3, 7.9 Hz), 7.52 (1H, dd, *J* = 4.9, 7.9 Hz), 7.57 - 7.66 (2H, m), 7.89 (1H, d, *J* = 7.9 Hz), 8.42 - 8.48 (1H, m), 8.73 (1H, dd, *J* = 1.9, 4.9 Hz), 9.32 (1H, d, *J* = 1.1 Hz), 12.36 (1H, s).

- 109 -

Example 2-2:*N*-(2,3-Dihydroimidazo[1,2-*c*]quinazolin-5-yl)nicotinamide hydrochloride

5

To a suspension of *N*-(2,3-dihydroimidazo[1,2-*c*]quinazolin-5-yl)nicotinamide (150 mg, 0.515 mmol) in tetrahydrofuran (4 ml) at 0°C was added a 4N solution of hydrochloric acid in 1,4-dioxane (2 ml, 8 mmol). The mixture was stirred at room temperature for 1 h, and concentrated under reduced pressure. The resulting residue was triturated with diethyl ether. The resulting precipitate was collected by filtration, washed with ethyl ether, and dried under reduced pressure to give *N*-(2,3-dihydroimidazo[1,2-*c*]quinazolin-5-yl)nicotinamide hydrochloride (192 mg, quantitative).

10

Melting point: 289°C (decomposition)

15 Mass spectrometry: 292

In vitro PI3K-β inhibitory activity: B

In vitro PI3K-γ inhibitory activity: A

¹H-NMR (300 MHz, DMSO-*d*₆): δ 4.18 - 4.30 (2H, m), 4.54 - 4.65 (2H, m), 7.56 - 7.65 (1H, m), 7.88 (1H, dd, *J* = 4.9, 7.9 Hz), 7.97 - 8.10 (2H, m), 8.64 (1H, d, *J* = 7.9 Hz), 8.80 (1H, d, *J* = 7.9 Hz), 8.95 (1H, dd, *J* = 1.5, 5.3 Hz), 9.43 (1H, d, *J* = 1.1 Hz), 12.7 - 13.3 (1H, br).

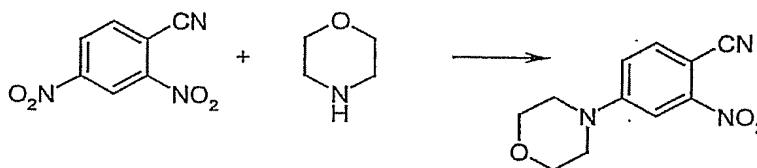
20

- 110 -

Example 2-3:

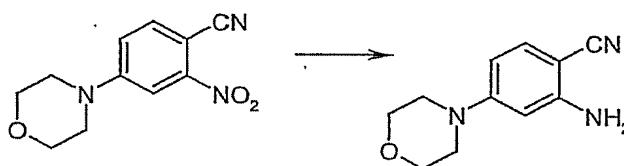
6-(Acetamido)-N-[8-(morpholin-4-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide

5 (1) 4-(Morpholin-4-yl)-2-nitrobenzonitrile



A mixture of 2,4-dinitrobenzonitrile 4.20g (21.75mmol) and morpholine 5.7mL (66.0mmol) in N,N-dimethylformamide 20mL was stirred at room temperature for 20 hours. The reaction mixture was poured into water. The precipitate was collected and washed with water to give the title compound 4.20g as orange solid. Yield 74.5%.

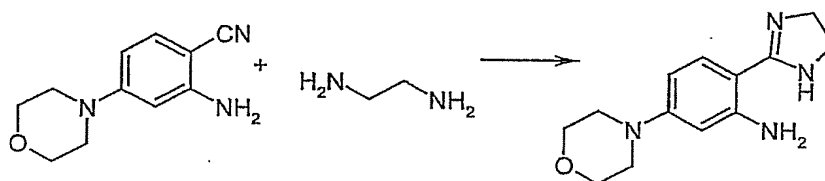
(2) 2-Amino-4-(morpholin-4-yl)benzonitrile



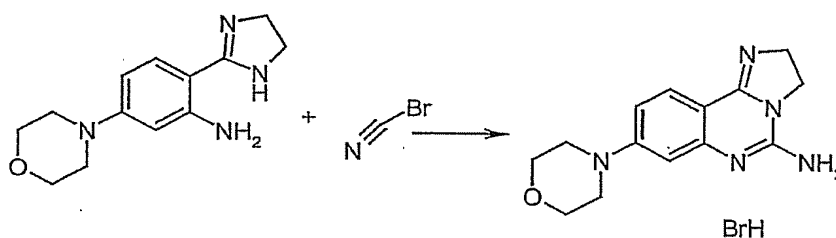
To a cooled mixture of tin(II) chloride dihydrate 12.8g (56.7mmol) in conc. HCl 40mL with ice bath was added 4-(morpholin-4-yl)-2-nitrobenzonitrile 4.20 g (16.09mmol) and stirred at room temperature for 2 hours. The reaction mixture was poured into diluted NaOH solution and extracted into ethyl acetate. The organic layer was washed with water and brine, dried over MgSO₄ and the solvent was evaporated. The crude product was washed with diethyl ether to give the title compound 3.13g as off-white solid. Yield 95.0%.

- 111 -

(3) [2-(4,5-dihydro-1H-imidazol-2-yl)-5-(morpholin-4-yl)phenyl]amine



To a solution of 2-amino-4-(morpholin-4-yl)benzonitrile 3.65g (18.0 mmol) in
5 ethylenediamine 20mL was added phosphorus pentasulfide 4.00mg (0.018 mmol)
and stirred at 140°C for 16 hours. After cooling to room temperature, the solvent was
evaporated. The residue was washed with water and diethyl ether to give the title
compound 3.70g as off-white solid. Yield 83.5%.

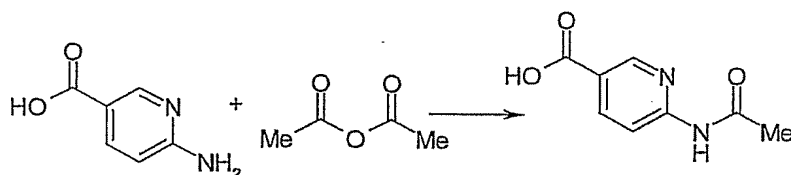
10 (4) 8-(Morpholin-4-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine
hydrobromide

15 To a suspension of [2-(4,5-dihydro-1H-imidazol-2-yl)-5-(morpholin-4-yl)phen-
yl]amine 3.60g (14.6mmol) in 2-propanol 20mL was added cyanogen bromide 2.32g
(21.9mmol) portionwise at 0°C and stirred at 100°C for 2 hours. After cooling to
room temperature, the precipitate was collected and washed with diethyl ether to give
the title compound 1.20g as yellow solid. Yield 77.5%.

20

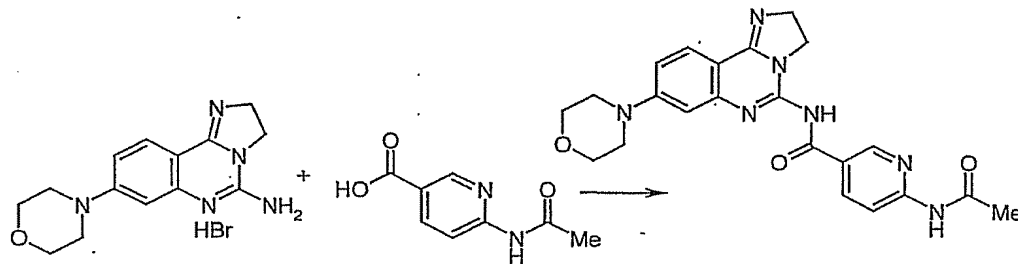
- 112 -

(5) 6-(Acetamido)nicotinic acid



A mixture of 6-aminonicotinic acid 5.00g (36.5mmol) and acetic anhydride 3.80mL (40.2mmol) in pyridine 30mL was stirred at 140°C for 24 hours. To the reaction mixture was added ethyl acetate and acidified with diluted HCl solution to pH 2. The organic layer was washed with water and brine, dried over MgSO₄, filtrated and the solvent was evaporated. The residue was washed with diisopropyl ether to give the title compound 1.70g as off-white solid. Yield 26%.

(6) 6-(Acetamido)-N-[8-(morpholin-4-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide



To a mixture of 8-(morpholin-4-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine hydrobromide 105.7mg (0.30mmol), 6-(acetamido)nicotinic acid 81.1mg (0.45mmol) and N,N-diisopropylethylamine 0.26mL (1.50mmol) in N,N-dimethylformamide 2 mL was added PyBOP((1H-1,2,3-benzotriazol-1-yloxy)(tripyrrolidin-1-yl)-phosphonium hexafluorophosphate) 234.2mg (0.45mmol) and stirred at 90°C for 16 hours. After cooling to room temperature, saturated NaHCO₃ solution was added. The precipitate was collected and washed with water, methanol, and diethyl ether to give the title compound 41.1mg as yellow solid. Yield 31.6%.

Melting point: 228°C

Mass spectrometry: 434

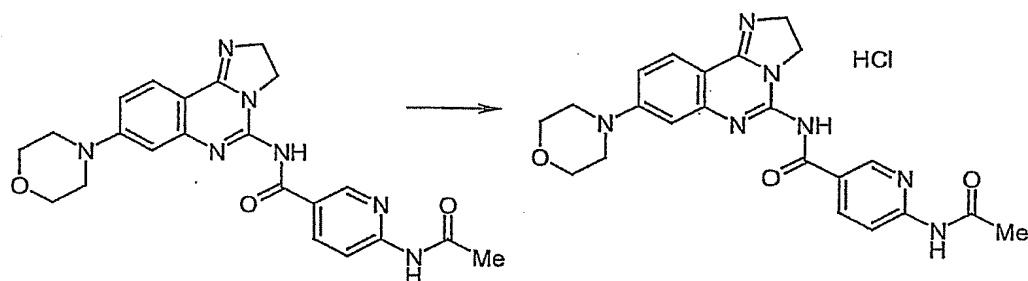
- 113 -

In vitro PI3K- β inhibitory activity: CIn vitro PI3K- γ inhibitory activity: A

5 H-NMR (500MHz, DMSO- d_6) δ : 3.22-3.30 (m 4H), 3.74 (s 3H), 3.86 (m 2H), 3.97 (m 2H), 6.77 (br s 1H), 7.60 (m 1H), 8.07 (m 1H), 8.32 (m 1H), 8.95 (br s 1H), 10.60 (s 1H)

Example 2-4:

10 6-(Acetamido)-N-[8-(morpholin-4-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide hydrochloride



15 To a mixture of 6-(acetamido)-N-[8-(morpholin-4-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide (Example 2-3) 20.0mg (0.046mmol) in 1,4-dioxane 1.5mL was added 4N HCl in 1,4-dioxane 0.5mL and stirred at room temperature for 40 minutes. The precipitate was collected and washed with diethyl ether to give the title compound 17.0mg as yellow solid. Yield 78%.

Melting point: 237°C

Mass spectrometry: 434

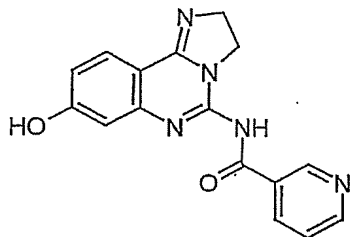
20 In vitro PI3K- β inhibitory activity: BIn vitro PI3K- γ inhibitory activity: A

25 H-NMR (500MHz, DMSO- d_6) δ : 3.41-3.76 (m 7H), 3.86 (m 2H), 4.10 (m 2H), 7.20 (m 1H), 7.39 (m 1H), 8.19 (m 1H), 8.45 (m 1H), 9.09 (br s 1H), 10.86 (s 1H)

- 114 -

Example 2-5:

N-(8-Hydroxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide



A suspension of N-(8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (example 2-22) 3.50g (10.9mmol) and sodium sulfide 4.25g (54.5mmol) in 1-methyl-2-pyrrolidinone 10mL was heated to 160°C for 4 hours (LC-MS indicated complete consumption of the starting material). The mixture was cooled to room temperature and volatile sideproducts were evaporated. The mixture was partitioned between chloroform and 0.5N NaOH solution. The aqueous layer was neutralized and the formed precipitate was collected to give the title compound 2.34g as off-white solid. Yield 69.9%.

Melting point: 289°C

Mass spectrometry: 308

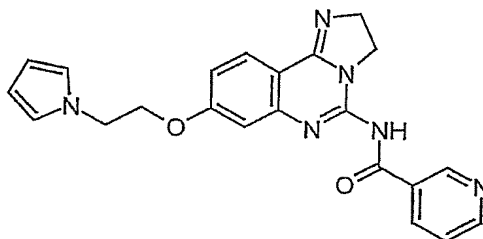
In vitro PI3K- β inhibitory activity: CIn vitro PI3K- γ inhibitory activity: B

H-NMR (500MHz, DMSO- d_6) δ : 4.01(m 2H), 4.15(m 2H), 6.75(dd 1H J=8Hz, 2Hz), 6.91(s 1H), 7.52(dd 1H J=8Hz, 5Hz), 7.75(d 1H J=8Hz), 8.44(d 1H J=8Hz), 8.73(dd 1H J=5Hz, 2Hz), 9.31(s 1H), 10.61(br s 1H), 12.24(br s 1H)

Example 2-6:

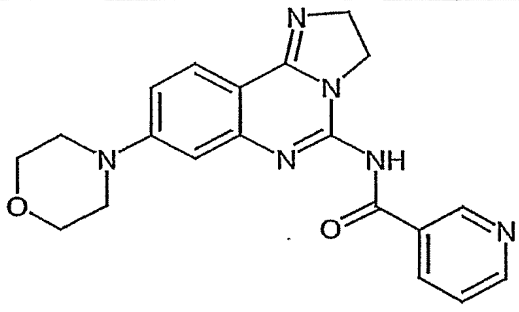
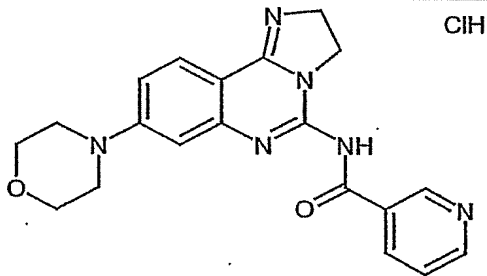
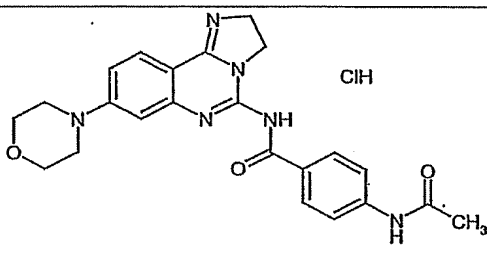
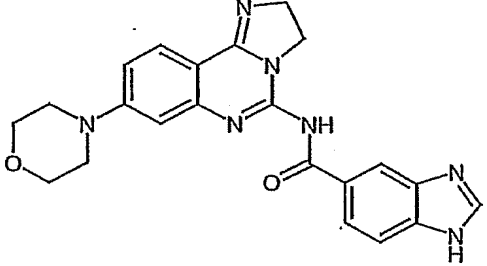
N-{8-[2-(1-pyrrolyl)ethoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide

- 115 -

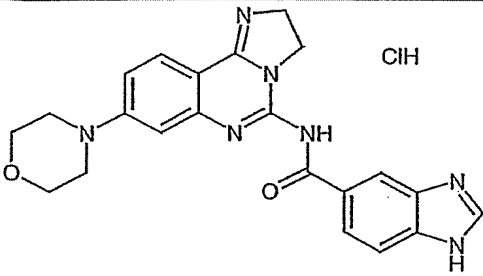
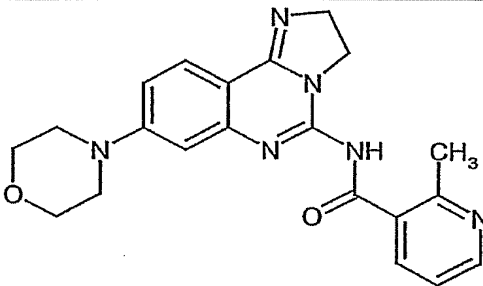
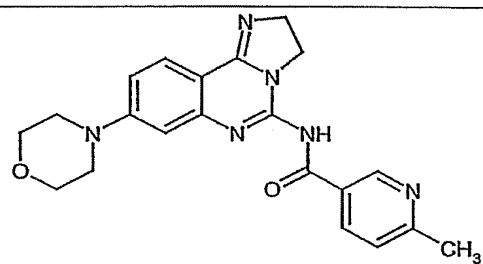
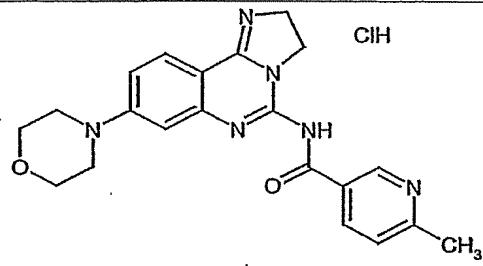
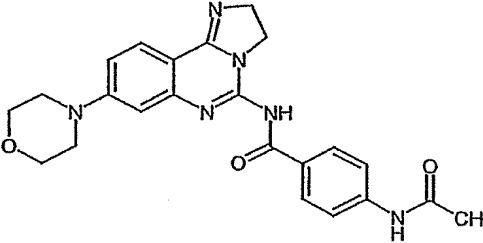


- The suspension of N-(8-Hydroxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (example 2-1) 70.0mg (0.23mmol), N-(2-bromoethyl)pyrrole 47.6mg (0.27mmol) and potassium carbonate 126mg (0.91mmol) in N,N-dimethylformamide 5mL was heated in a sealed tube to 120°C for 3 hours. The reaction mixture was concentrated and partitioned between dichloromethane and water. The organic layer was washed with 0.1N NaOH solution and brine, dried over Na₂SO₄ and the solvent was evaporated to give the title compound 49.0mg as off-white solid. Yield 54%.
- 10 Melting point: 209°C
Mass spectrometry: 401
In vitro PI3K-β inhibitory activity: B
In vitro PI3K-γ inhibitory activity: B
- 15 ¹H-NMR (500MHz, DMSO-d₆) δ: 4.00(m 2H), 4.12(m 2H), 4.30(s 4H), 6.00(m 2H), 6.84(m 2H), 6.85(dd 1H J=6Hz, 2Hz), 7.27(d 1H J=2Hz), 7.52(dd 1H J=6Hz), 7.76(d 1H J=8Hz), 8.44(dd 1H J=8Hz, 2Hz), 8.72(dd 1H J=5Hz, 2Hz), 9.31(s 1H), 12.32(s 1H)
- 20 In a similar method according to the Example 2-1 to 2-6 above, the compounds in Example 2-7 to 2-368 were synthesized.

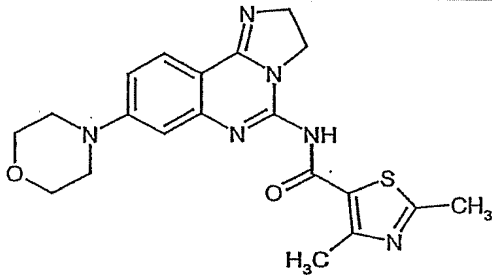
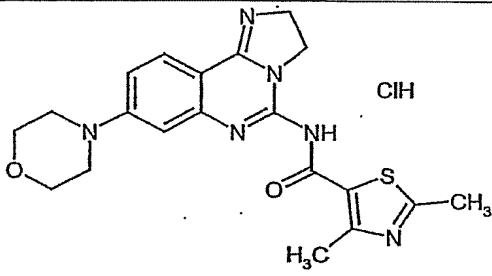
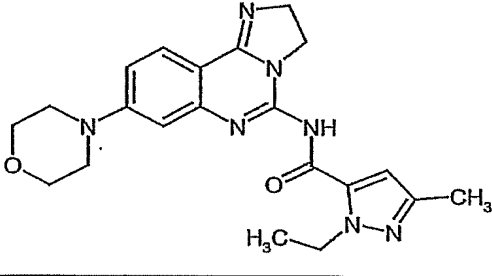
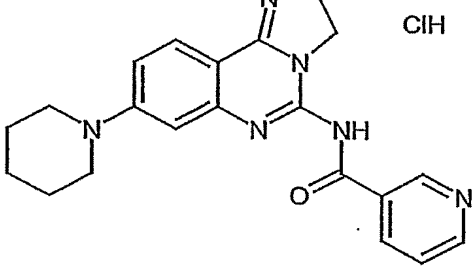
Table 2

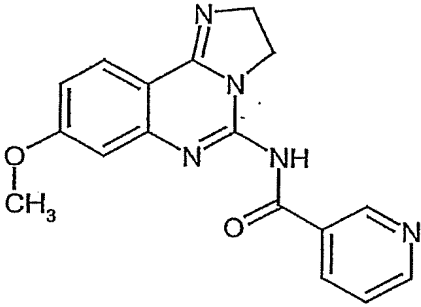
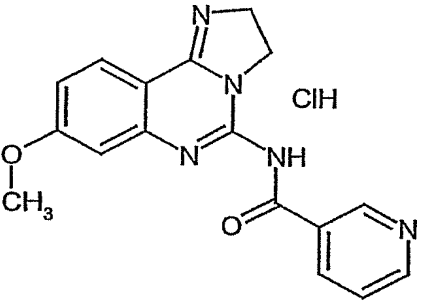
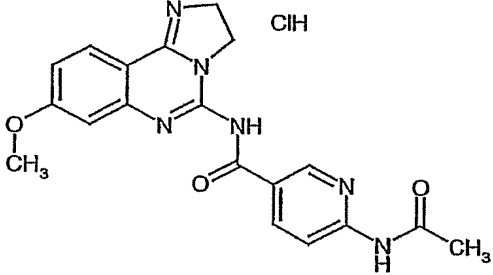
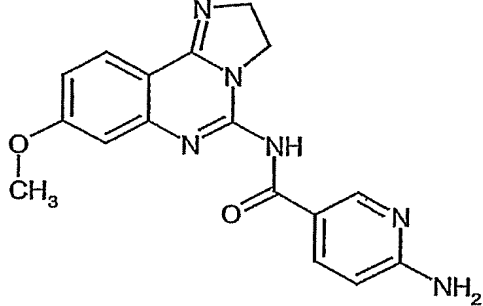
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-7		376,42	377	243	B
2-8		412,88	377	283	A
2-9		468,95	433	249	B
2-10		415,46	416	250(dec.)	B

- 117 -

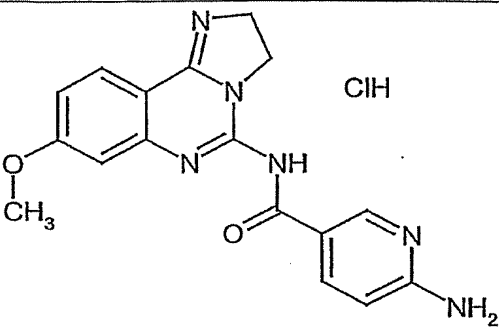
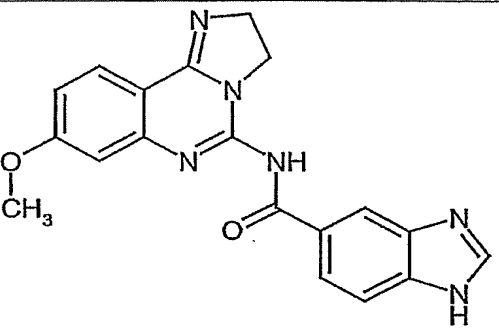
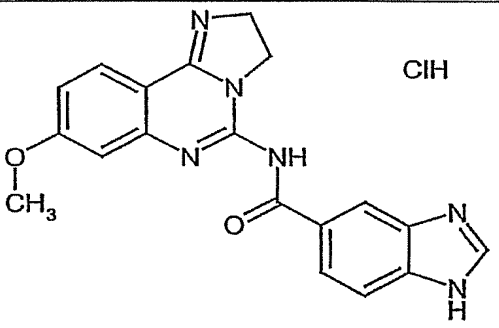
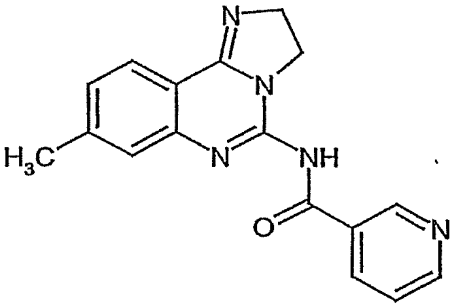
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-11	 ClH	451,92	416	294(dec.)	A
2-12		390,45	391	199(dec.)	B
2-13		390,45	391	209	A
2-14	 ClH	426,91	391	267(dec.)	A
2-15		432,49	433	227	B

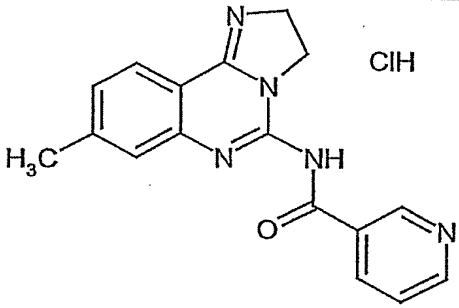
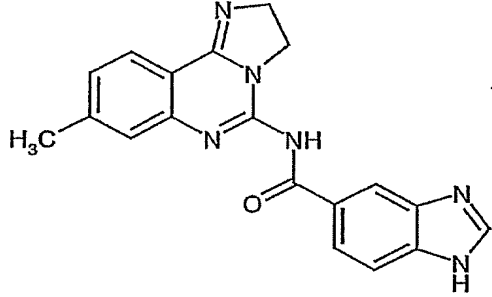
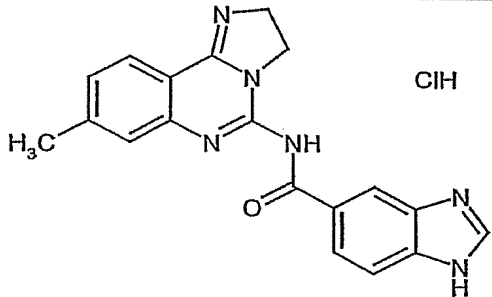
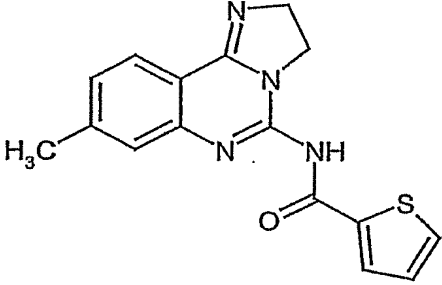
- 118 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-16		410,50	411	233(dec.)	B
2-17		446,96	411	255(dec.)	A
2-18		407,48	408	232	B
2-19		410,91	376	>300	B

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-20		321,34	322	281(dec.)	B
2-21		357,80	322	292(dec.)	B
2-22		414,85	379	198-205(dec.)	B
2-23		336,36	337	279-282	A

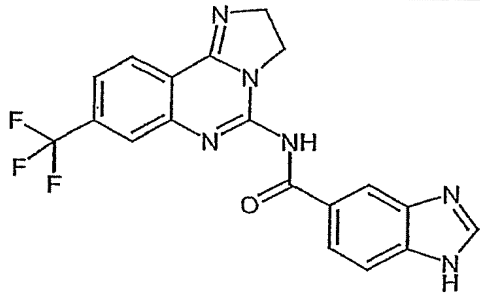
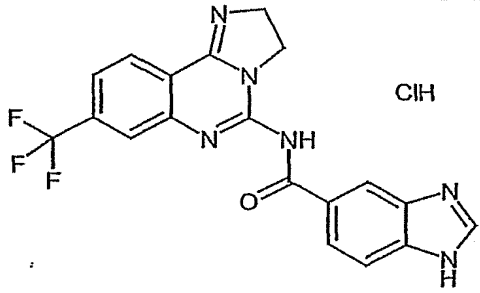
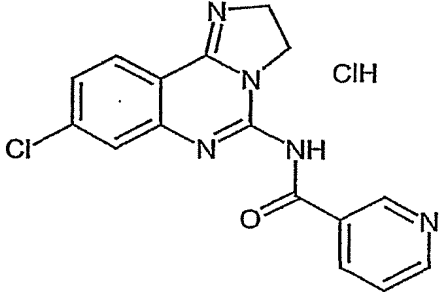
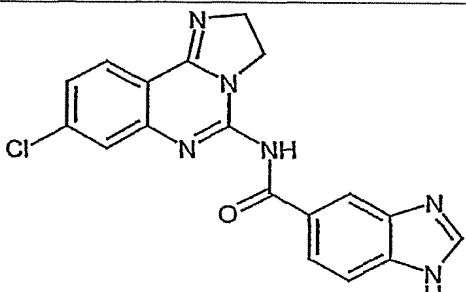
- 120 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-24	 ClH	372,82	337	273(dec.)	A
2-25		360,38	361	186	A
2-26	 ClH	396,84	361	233	A
2-27		305,34	306	207	A

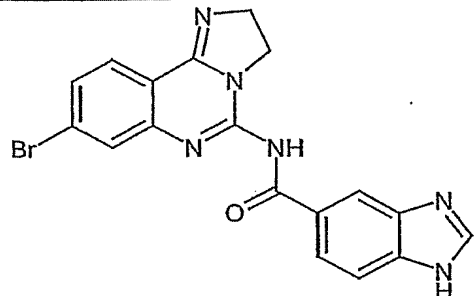
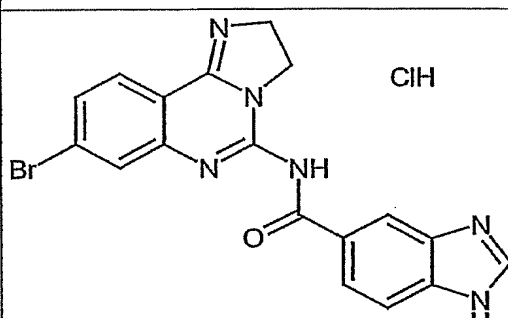
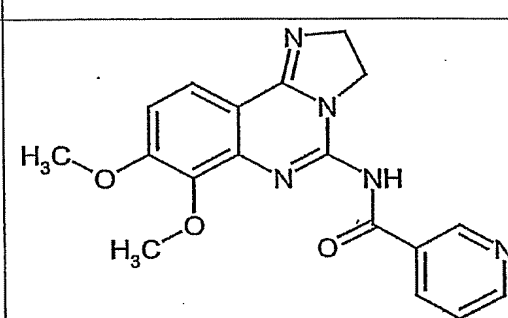
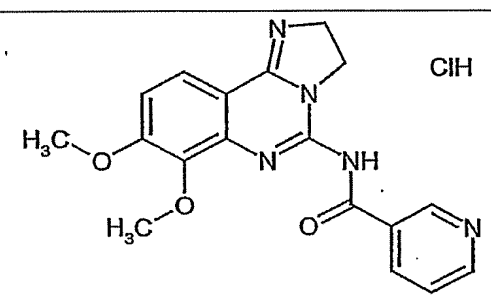
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-28	 ClH	341,80	306	315	A
2-29		344,38	345	190	A
2-30	 ClH	380,84	345	295	B
2-31		310,38	311	182	B

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-32	 <chem>Cc1ccc2nc3c(nc21)C(=O)Nc4ccsc4</chem> ClH	346,84	311	276	B
2-33	 <chem>Fc1cc(F)c(F)cc2nc3c(nc21)C(=O)Nc4ccncc4</chem>	359,31	360	229	B
2-34	 <chem>Fc1cc(F)c(F)cc2nc3c(nc21)C(=O)Nc4ccncc4</chem> ClH	395,77	360	275	A
2-35	 <chem>Fc1cc(F)c(F)cc2nc3c(nc21)C(=O)Nc4cc(O)cn4</chem> ClH	411,77	375	237(dec.)	A

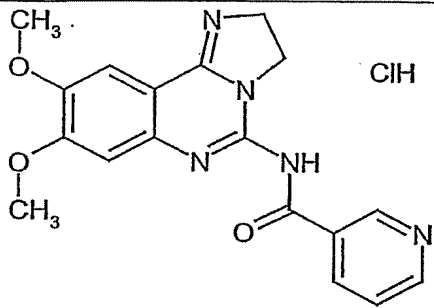
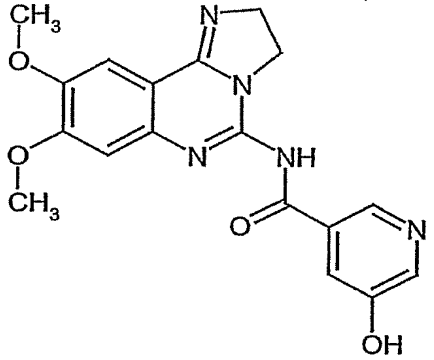
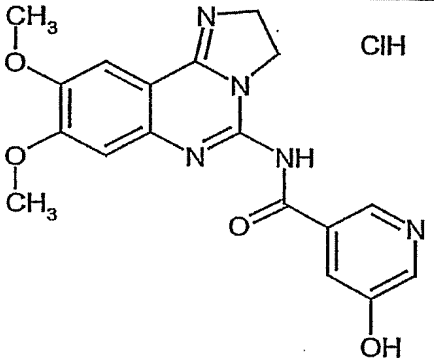
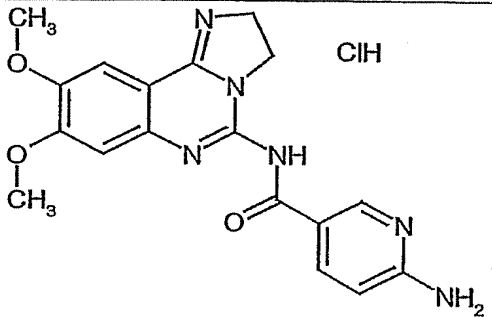
- 123 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-36		398,35	399	>300	B
2-37		434,81	399	288	A
2-38		362,22	327	308	B
2-39		364,80	366	288	A

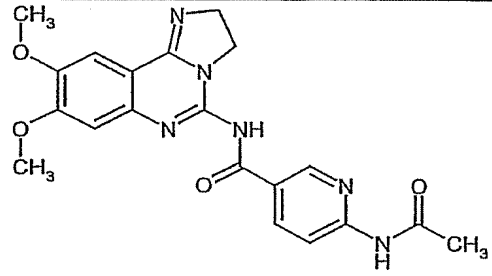
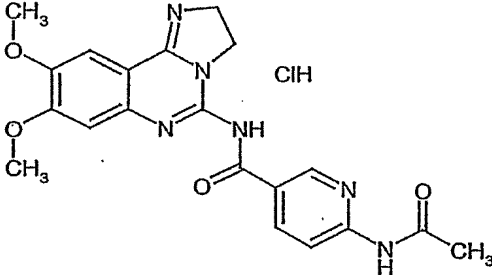
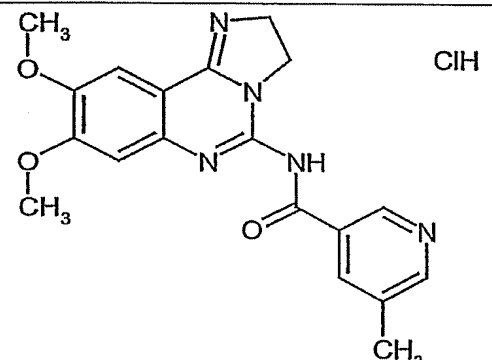
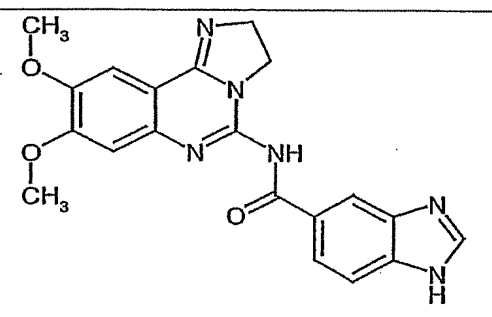
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-40	 ClH	401,26	366	270	A
2-41	 ClH	367,26	332	328	B
2-42	 ClH	406,67	372, 370	243	A
2-43	 ClH	420,70	386, 384	252(dec.)	B

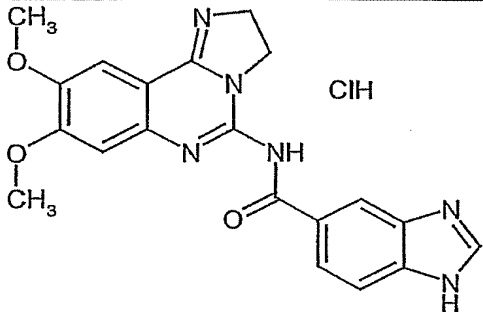
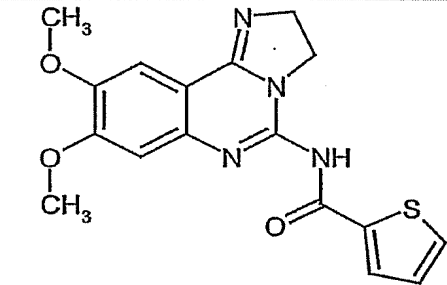
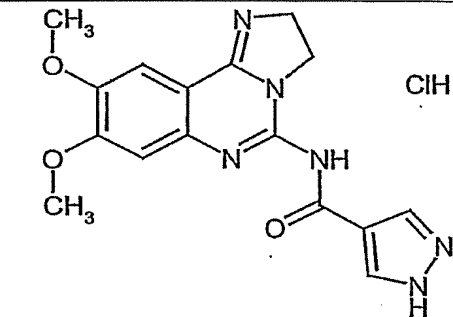
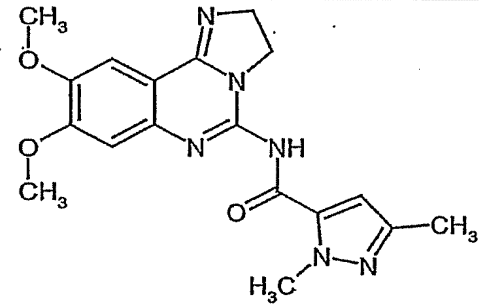
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-44		409,25	411, 409	262	B
2-45		445,71	411, 409	278	A
2-46		351,37	352	259-260	A
2-47		387,83	352	257-257	A

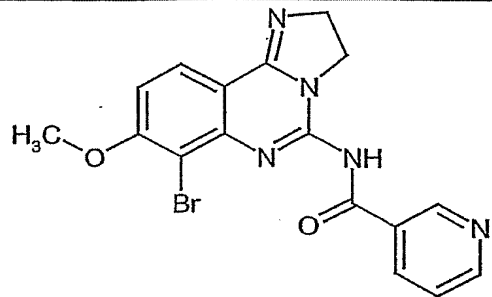
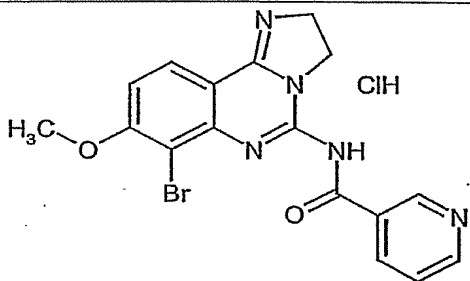
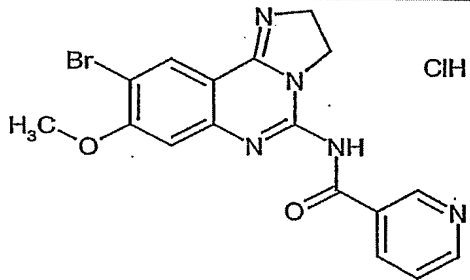
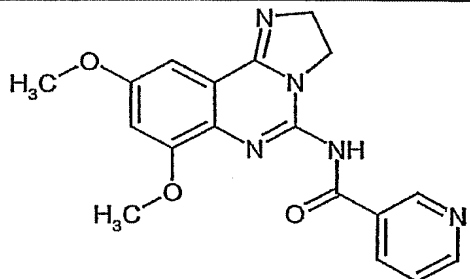
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-48		408,42	409	306-307	A
2-49		390,40	391	289(dec.)	A
2-50		426,87	391	278(dec.)	A
2-51		391,39	392	233(dec.)	A
2-52		427,85	392	210(dec.)	A

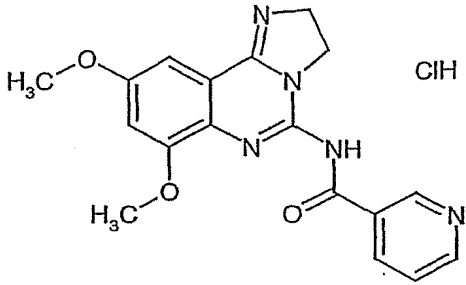
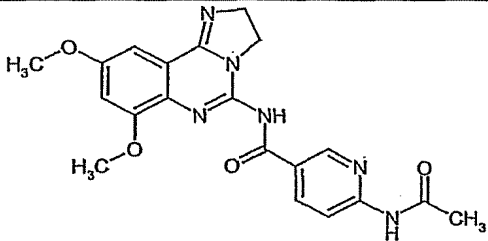
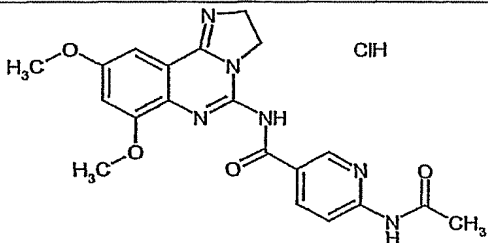
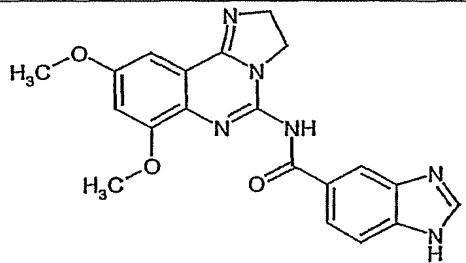
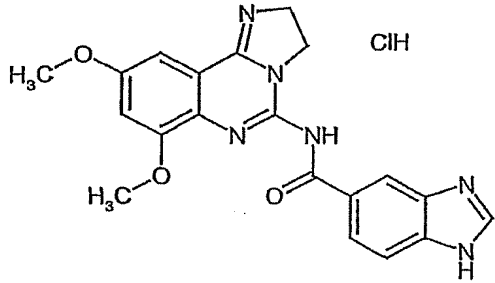
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-53	 ClH	387,83	352	246	B
2-54	 ClH	367,37	367	287(dec.)	A
2-55	 ClH	403,83	367	260(dec.)	A
2-56	 ClH	402,84	367	256	B

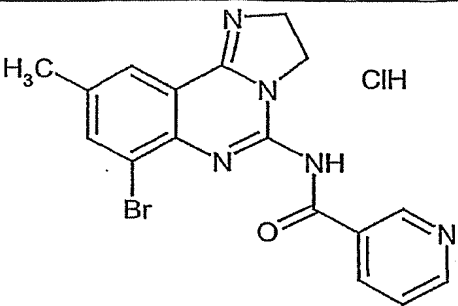
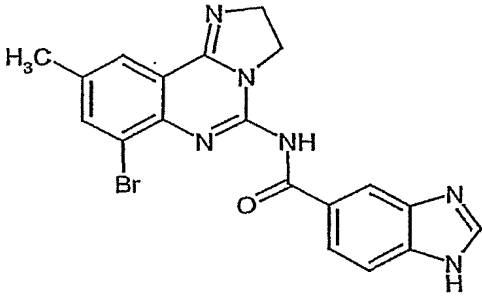
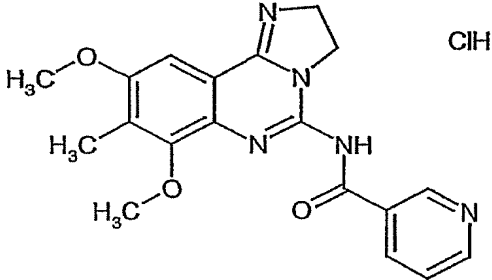
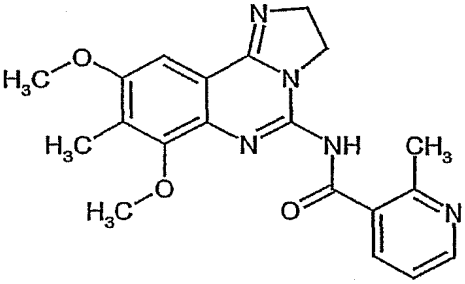
- 128 -

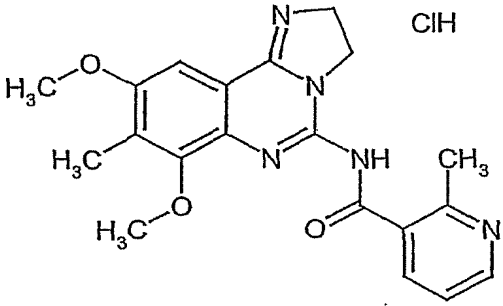
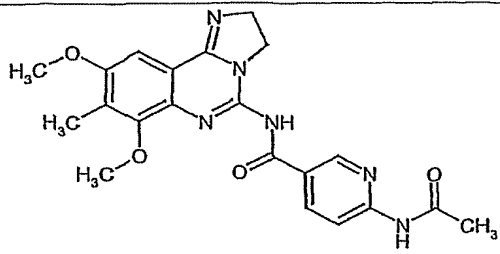
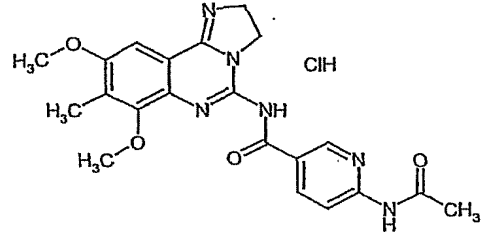
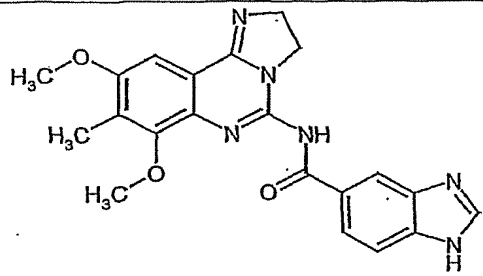
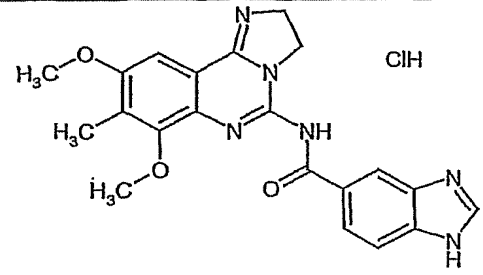
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-57		408,42	409	224	B
2-58		444,88	409	279	B
2-59		401,86	366	257(dec.)	B
2-60		390,40	391	246	A

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-61	 ClH	426,87	391	276	A
2-62		356,41	357	248	B
2-63	 ClH	376,81	340	270(dec.)	B
2-64	 H ₃ C	368,40	368	236-237	B

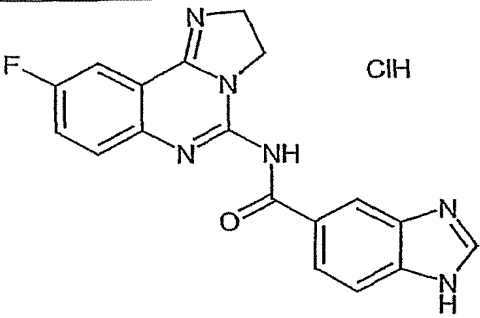
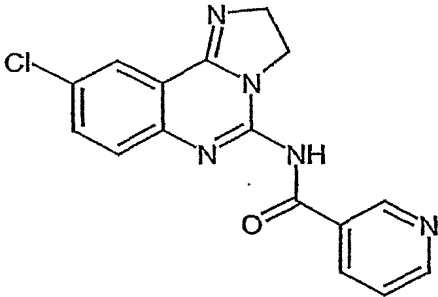
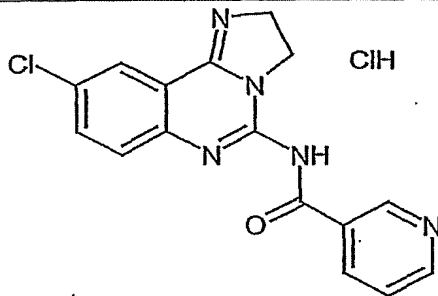
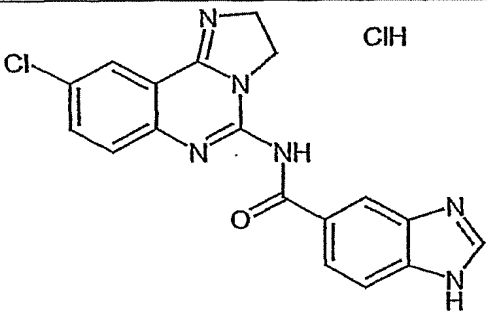
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-65		400,24	402, 400	264	A
2-66		436,70	402, 400	298	A
2-67		436,70	402, 400	289(dec.)	B
2-68		351,37	352	228(dec.)	A

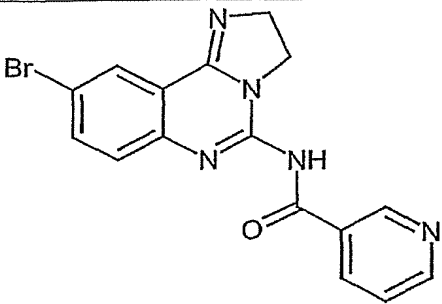
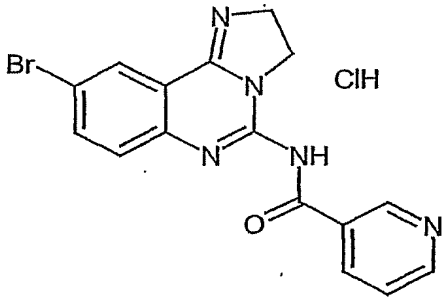
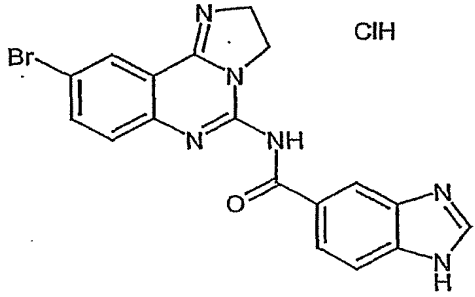
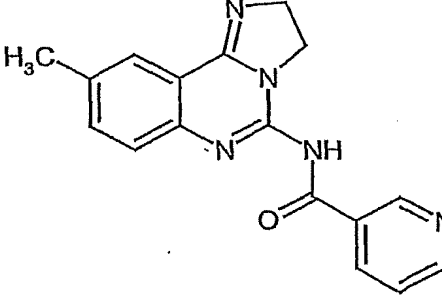
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-69	 <chem>COc1cc(OC)cc(cc1C2=NC3CCN=C3N2C(=O)Nc4ccncc4)C5=CC=CC=N5.[Cl-]</chem>	387,83	352	275(dec.)	B
2-70	 <chem>COc1cc(OC)cc(cc1C2=NC3CCN=C3N2C(=O)Nc4cc(C(=O)N)ccn4)C5=CC=CC=N5</chem>	408,42	408	286(dec.)	B
2-71	 <chem>COc1cc(OC)cc(cc1C2=NC3CCN=C3N2C(=O)Nc4cc(C(=O)N)ccn4)C5=CC=CC=N5.[Cl-]</chem>	444,88	408	270(dec.)	B
2-72	 <chem>COc1cc(OC)cc(cc1C2=NC3CCN=C3N2C(=O)Nc4c5ccncc5cc4)C6=CC=CC=N6</chem>	390,40	391	210(dec.)	A
2-73	 <chem>COc1cc(OC)cc(cc1C2=NC3CCN=C3N2C(=O)Nc4c5ccncc5cc4)C6=CC=CC=N6.[Cl-]</chem>	426,87	391	289(dec.)	A

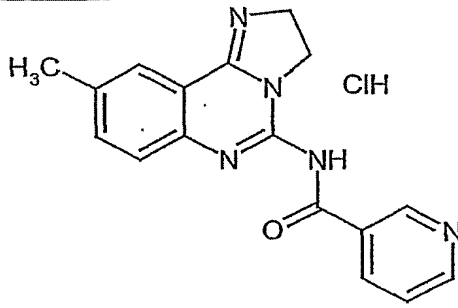
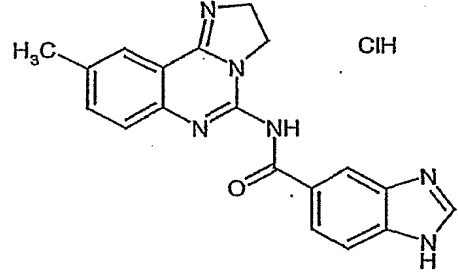
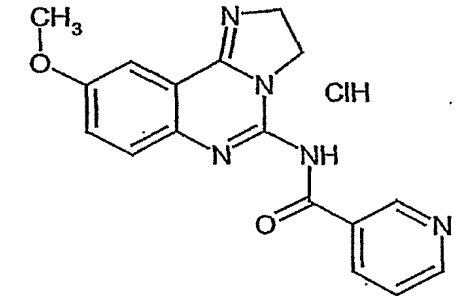
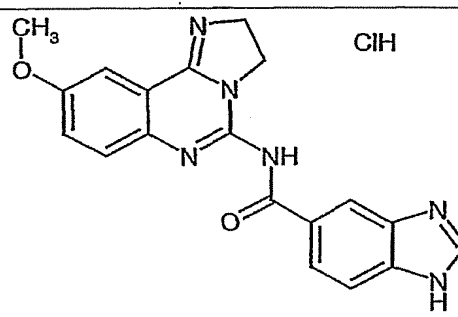
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-74	 <chem>Cc1cc(Br)ccc2nc3c(ncn3C)nc(NC(=O)c4ccncc4)c2</chem> ClH	420,70	386, 384	220	A
2-75	 <chem>Cc1cc(Br)ccc2nc3c(ncn3C)nc(NC(=O)c4ccc5c(c4)ncn5)c2</chem>	423,28	425, 423	>290	B
2-76	 <chem>COc1cc(OC)c(C)cc2nc3c(ncn3C)nc(NC(=O)c4ccncc4)c12</chem> ClH	401,86	366	235(dec.)	B
2-77	 <chem>Cc1cc(C)cc(OC)c2nc3c(ncn3C)nc(NC(=O)c4cc(C)cn4)c12</chem>	379,42	379	210(dec.)	A

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-78	 <chem>COc1cc2c(c1)nc3c2n(c3)C(=O)Nc4cc(C)ncn4</chem> ClH	415,88	379	230(dec.)	A
2-79	 <chem>CC(=O)Nc1ccc(cc1)C(=O)Nc2nc3c(c2)nc4c3c(c1)nc5c4c3c2n(c5)C(=O)Nc6cc(C)ncn6</chem>	422,45	422	> 310	B
2-80	 <chem>CC(=O)Nc1ccc(cc1)C(=O)Nc2nc3c(c2)nc4c3c(c1)nc5c4c3c2n(c5)C(=O)Nc6cc(C)ncn6</chem> ClH	458,91	422	305(dec.)	A
2-81	 <chem>COc1cc2c(c1)nc3c2n(c3)C(=O)Nc4c5ccccc4[nH]5</chem>	404,43	405	202	B
2-82	 <chem>COc1cc2c(c1)nc3c2n(c3)C(=O)Nc4c5ccccc4[nH]5</chem> ClH	440,89	405	280(dec.)	B

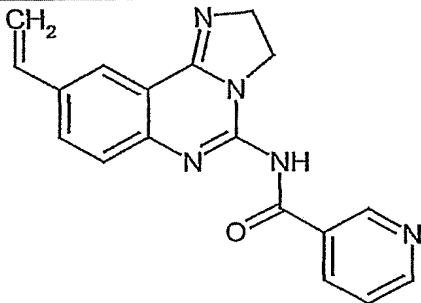
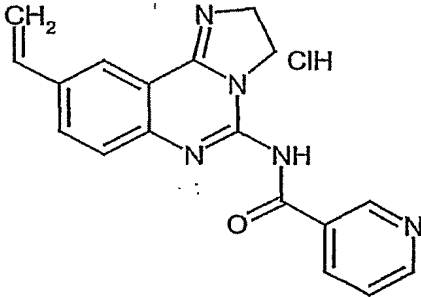
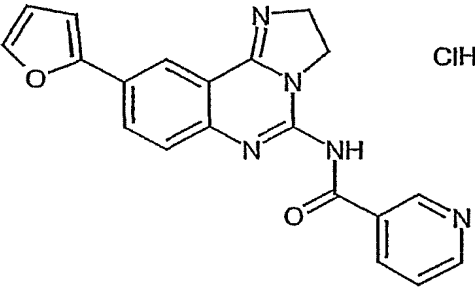
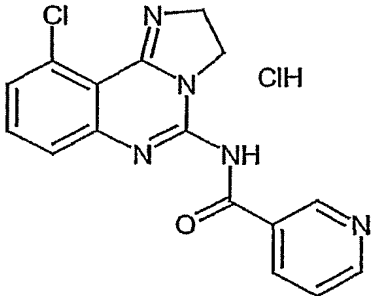
- 134 -

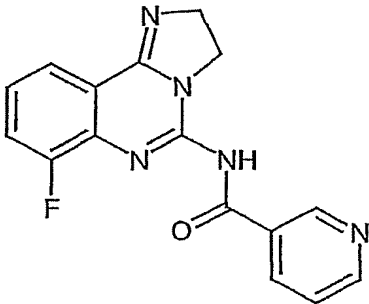
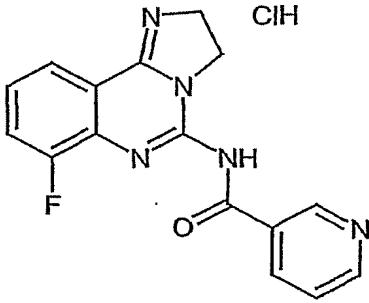
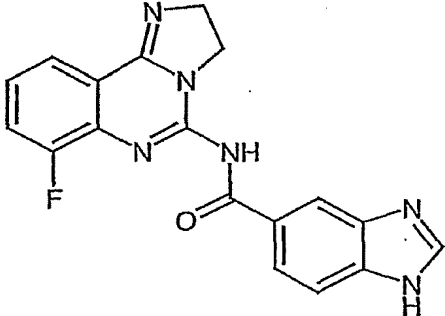
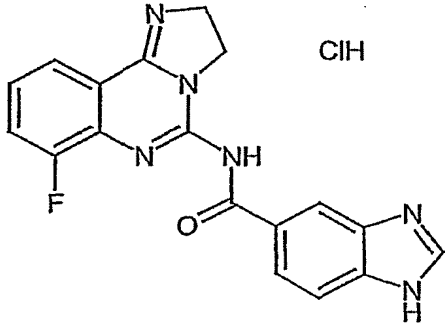
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-83	 ClH	384,80	349	>300	B
2-84		325,76	326	210	B
2-85	 ClH	362,22	327	309	B
2-86	 ClH	401,26	366	305(dec.)	B

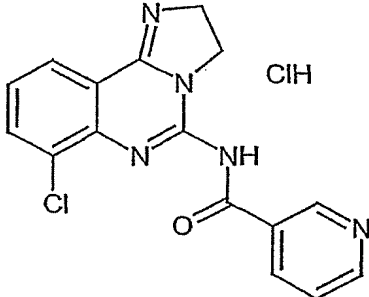
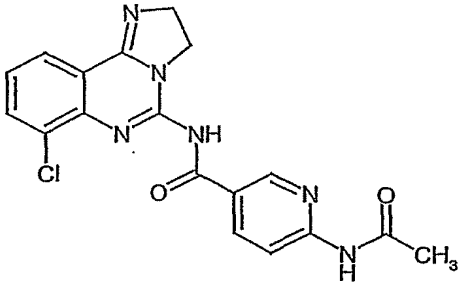
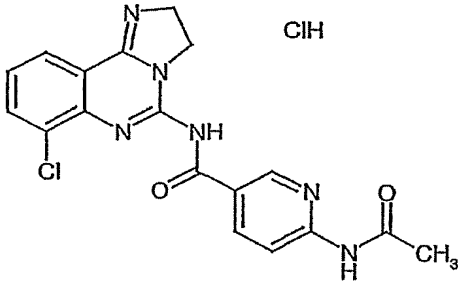
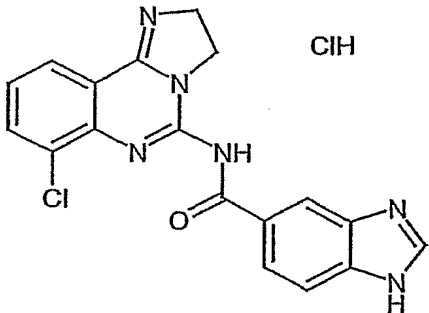
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-87		370,21	372	228	B
2-88	 ClH	406,67	372, 370	316	B
2-89	 ClH	445,71	411, 409	288	B
2-90		305,34	306	210	A

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-91	 <chem>Cc1ccc2nc3c(nc2c1)nn3NC(=O)c4cccnc4.Cl</chem>	341,80	306	>290	B
2-92	 <chem>Cc1ccc2nc3c(nc2c1)nn3NC(=O)c4ccc5c(c4)nn[nH]5.Cl</chem>	380,84	345	>290	A
2-93	 <chem>COc1ccc2nc3c(nc2c1)nn3NC(=O)c4cccnc4.Cl</chem>	357,80	322	>300	B
2-94	 <chem>COc1ccc2nc3c(nc2c1)nn3NC(=O)c4ccc5c(c4)nn[nH]5.Cl</chem>	396,84	361	288	A

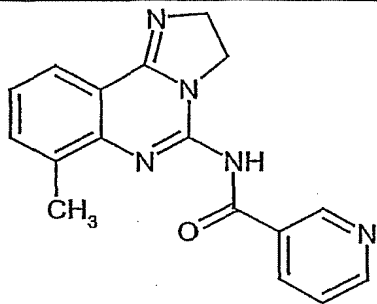
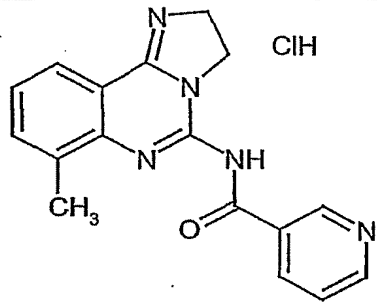
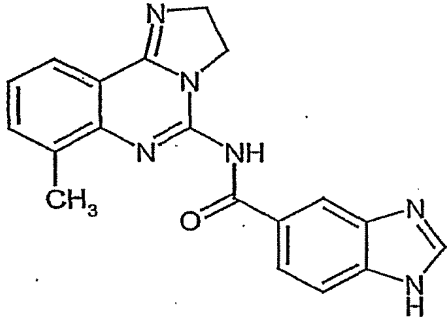
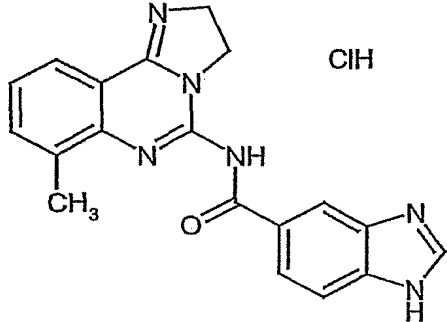
- 137 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-95		317,35	318	196-198	B
2-96		353,81	318	275-277	B
2-97		393,84	358	298-299	B
2-98		362,22	327	249	B

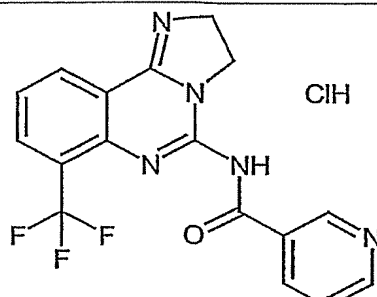
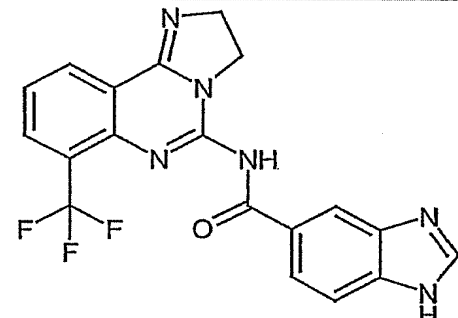
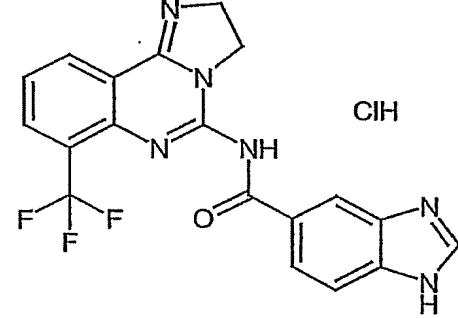
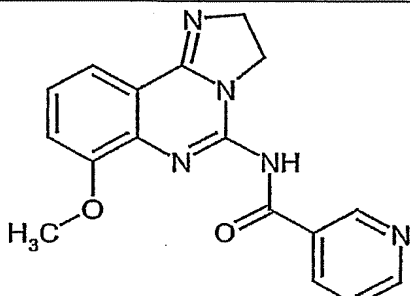
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-99		309,31	310	243	B
2-100		345,77	310	288	A
2-101		348,34	349	>300	A
2-102		384,80	349	>300	A

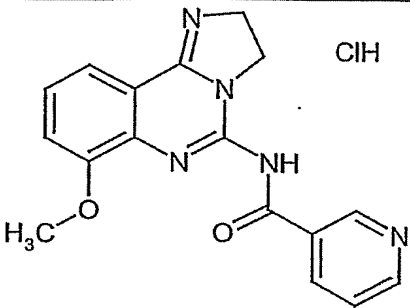
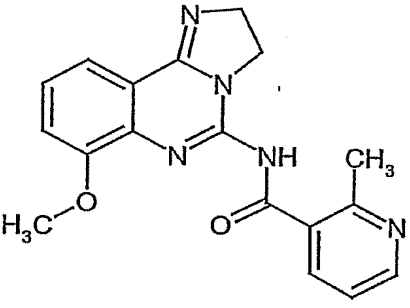
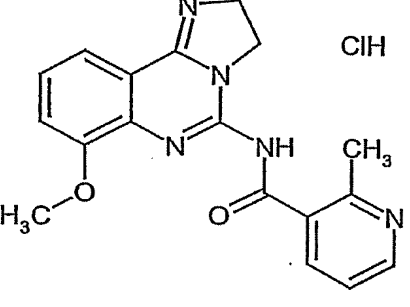
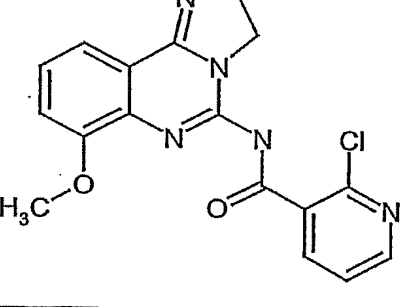
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-103	 ClH	362,22	326	>280	B
2-104	 ClH	382,81	383	> 280	B
2-105	 ClH	419,27	383	> 280	A
2-106	 ClH	401,26	365	> 280	B

- 140 -

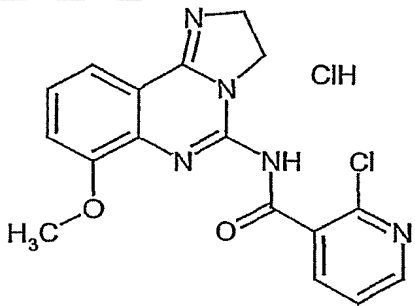
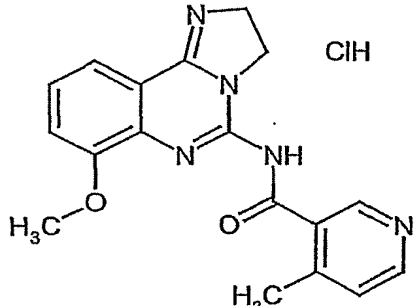
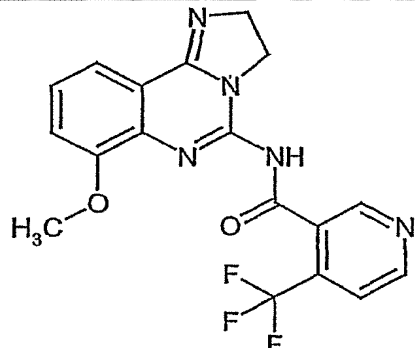
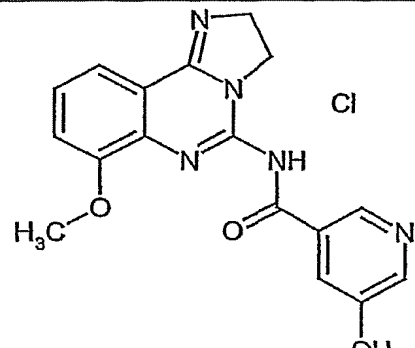
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-107		305,34	306	244	B
2-108		341,80	306	>290	B
2-109		344,38	345	>290	A
2-110		380,84	345	>290	A

- 141 -

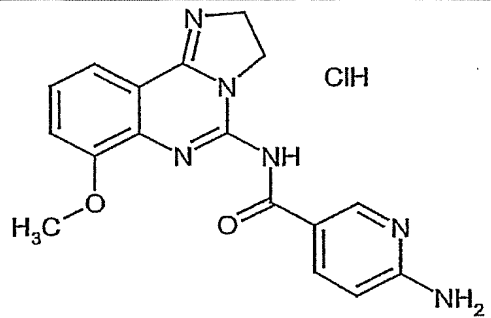
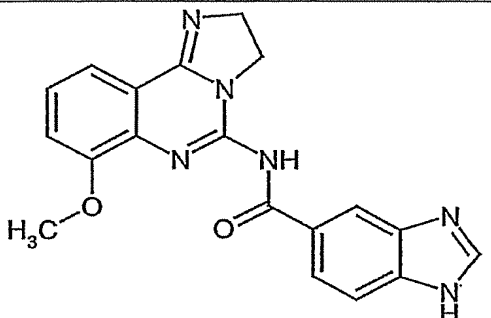
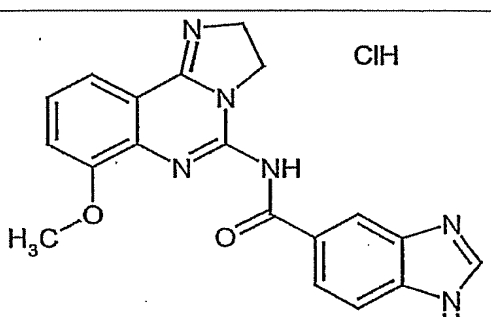
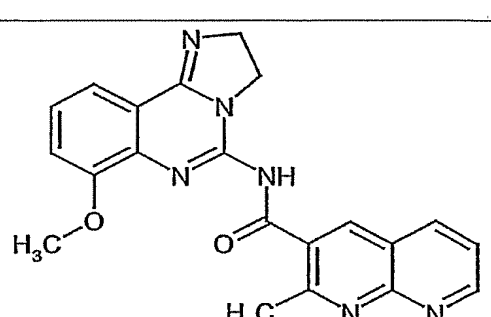
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-111	 ClH	395,77	360	263	A
2-112		398,35	399	286	A
2-113	 ClH	434,81	399	270	A
2-114	 H ₃ C-O	321,34	322	110	A

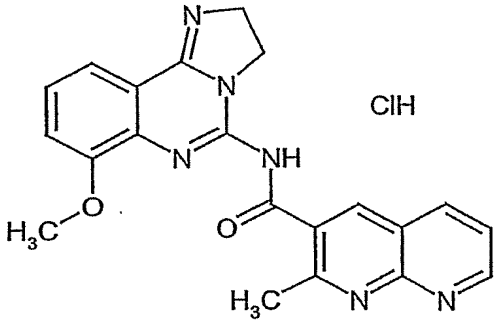
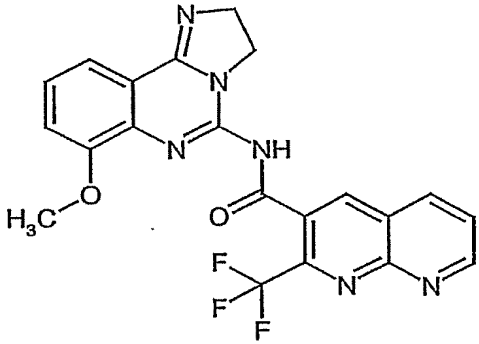
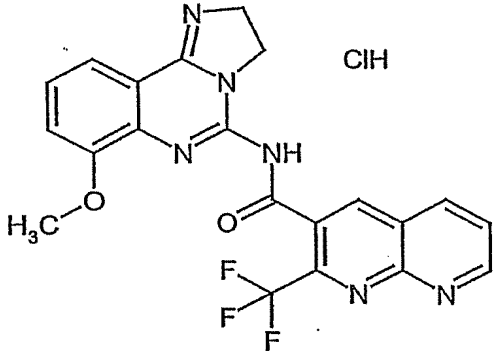
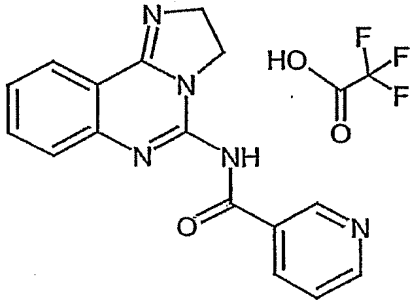
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-115	 <chem>COC1=CC=C(C=C1)N2C(=N3C(=N2)CCN3)C(=O)Nc4cccnc4.Cl</chem>	357,80	322	237(dec.)	A
2-116	 <chem>COC1=CC=C(C=C1)N2C(=N3C(=N2)CCN3)C(=O)Nc4cc(C)nc(C)n4</chem>	335,37	335	204-205	B
2-117	 <chem>COC1=CC=C(C=C1)N2C(=N3C(=N2)CCN3)C(=O)Nc4cc(C)nc(C)n4.Cl</chem>	371,83	335	251(dec.)	A
2-118	 <chem>COC1=CC=C(C=C1)N2C(=N3C(=N2)CCN3)C(=O)Nc4cc(Cl)nc(C)n4</chem>	355,79	355	185(dec)	A

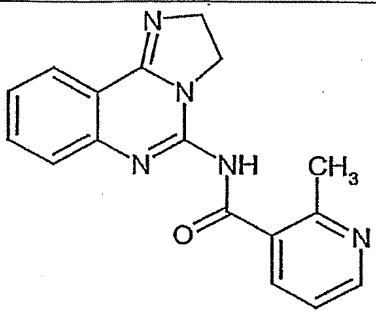
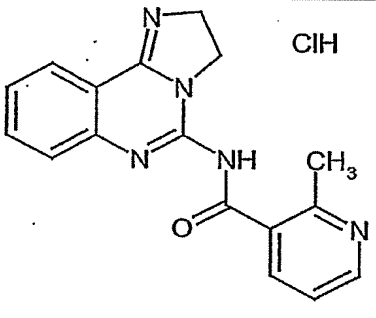
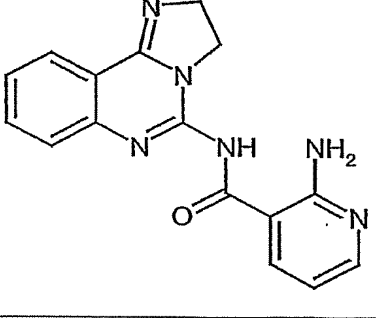
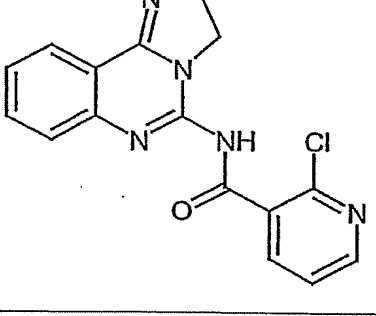
- 143 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-119	 <chem>COc1ccc2nc3c(ncn3C2)c4cc(Cl)ccn4</chem> ClH	392,25	355	266(dec.)	A
2-120	 <chem>COc1ccc2nc3c(ncn3C2)c4cc(C)ccn4</chem> ClH	371,83	335	220 (dec.)	A
2-121	 <chem>COc1ccc2nc3c(ncn3C2)c4cc(C(F)(F)F)ccn4</chem>	389,34	389	144-145	B
2-122	 <chem>COc1ccc2nc3c(ncn3C2)c4cc(O)ccn4</chem> Cl	373,80	338	285(dec.)	A

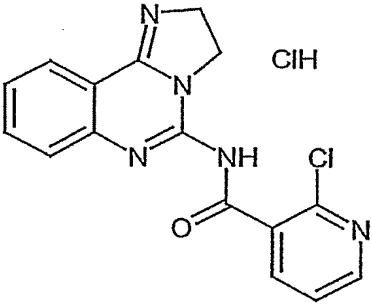
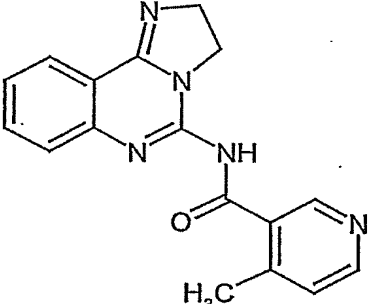
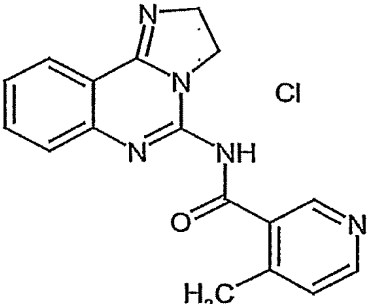
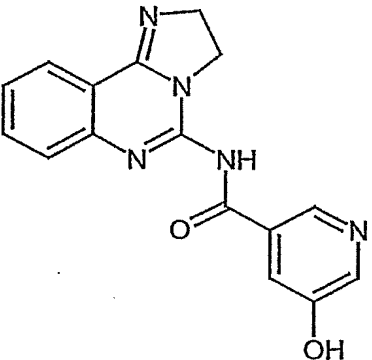
- 144 -

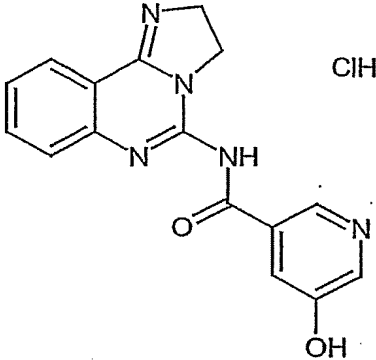
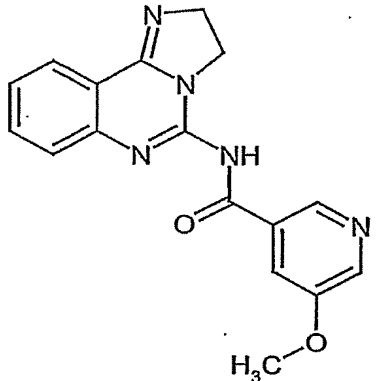
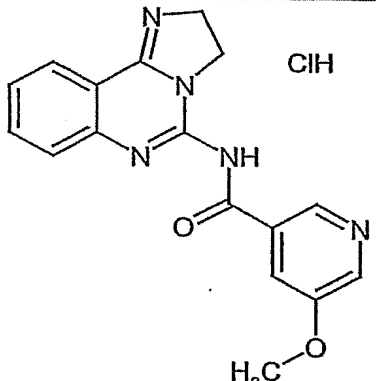
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-123	 <chem>COc1ccc2nc3c(ncn3C4=CC=C(N)C=C4)c5ccccc25.Cl</chem>	372,82	337	296	A
2-124	 <chem>COc1ccc2nc3c(ncn3C4=Cc5c[nH]cnc5C=C4)c6ccccc26</chem>	360,38	361	287	A
2-125	 <chem>COc1ccc2nc3c(ncn3C4=Cc5c[nH]cnc5C=C4)c6ccccc26.Cl</chem>	396,84	361	238	A
2-126	 <chem>COc1ccc2nc3c(ncn3C4=Cc5cnc6c(C)ncnc56)c7ccccc27</chem>	386,42	386	183-184	A

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-127	 <chem>COc1ccc(cc1)c2nc3c(ncn3C(=O)Nc4ccc5c(c4)ncn5C)c6ccccc6</chem> ClH	422,88	386	225 (dec.)	A
2-128	 <chem>COc1ccc(cc1)c2nc3c(ncn3C(=O)Nc4ccc5c(c4)ncn5C(F)(F)F)c6ccccc6</chem>	440,39	440	214 (dec.)	A
2-129	 <chem>COc1ccc(cc1)c2nc3c(ncn3C(=O)Nc4ccc5c(c4)ncn5C(F)(F)F)c6ccccc6</chem> ClH	476,85	440	226 (dec.)	A
2-130	 <chem>COc1ccc(cc1)c2nc3c(ncn3C(=O)Nc4ccncc4)C(F)(F)F(=O)O</chem>	405,34	292	237-239	A

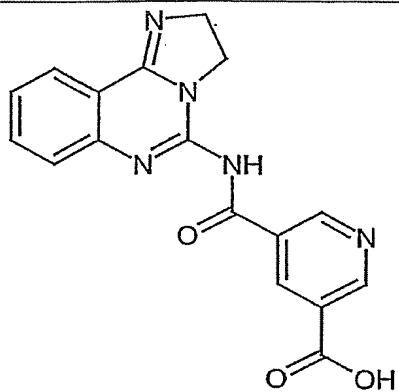
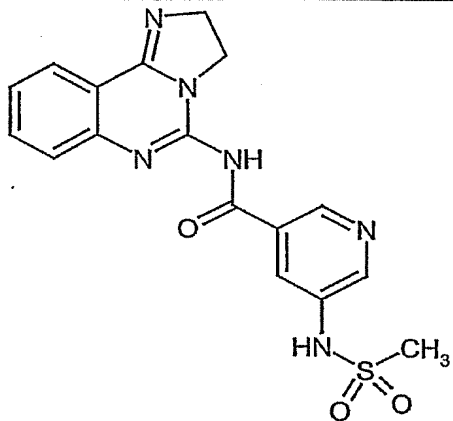
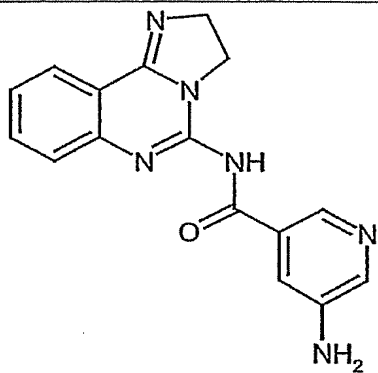
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-131	 <chem>Cc1ccncc1NC(=O)N2C=NC3=CC=CC=C3N2</chem>	305,34	306	193 - 194	B
2-132	 <chem>Cc1ccncc1NC(=O)N2C=NC3=CC=CC=C3N2.Cl</chem>	341,80	306	277 (dec.)	B
2-133	 <chem>Nc1ccncc1NC(=O)N2C=NC3=CC=CC=C3N2</chem>	306,33	306	215(dec.)	B
2-134	 <chem>Clc1ccncc1NC(=O)N2C=NC3=CC=CC=C3N2</chem>	325,76	326	198 - 199	A

- 147 -

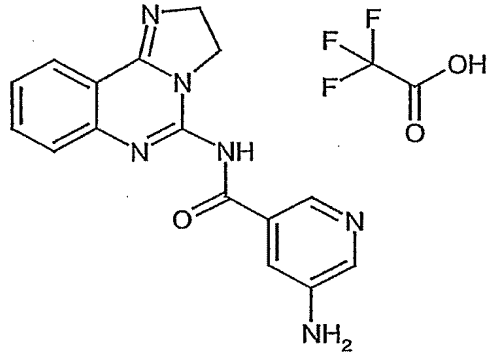
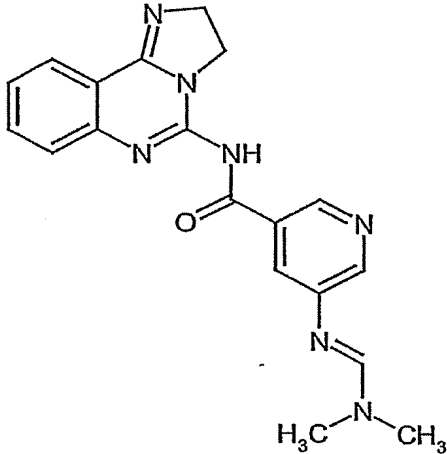
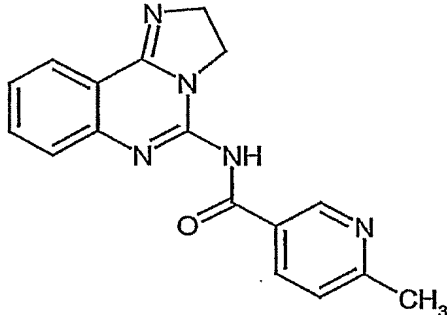
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-135	 <chem>Clc1ccc(cc1)C(=O)Nc2nc3ccccc3n2C4CCN4</chem> ClH	362,22	326	340 (dec.)	B
2-136	 <chem>Cc1cccc(c1)C(=O)Nc2nc3ccccc3n2C4CCN4</chem>	305,34	305	194-195	B
2-137	 <chem>Cc1cccc(c1)C(=O)Nc2nc3ccccc3n2C4CCN4</chem> Cl	341,80	305	291 (dec.)	B
2-138	 <chem>Oc1ccc(cc1)C(=O)Nc2nc3ccccc3n2C4CCN4</chem>	307,31	307	273(dec.)	A

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-139	 <chem>ClC1=NC2=C(NC(=O)c3cc(O)cn3)N3CCN=C3C2=CC=C1</chem>	343,78	307	296-297	A
2-140	 <chem>COc1cc(C(=O)Nc2nc3c(ncn3C2=CC=C1)cn)cn1</chem>	321,34	321	219 (dec.)	B
2-141	 <chem>COc1cc(C(=O)Nc2nc3c(ncn3C2=CC=C1)cn)cn1</chem>	357,80	321	272(dec.)	B

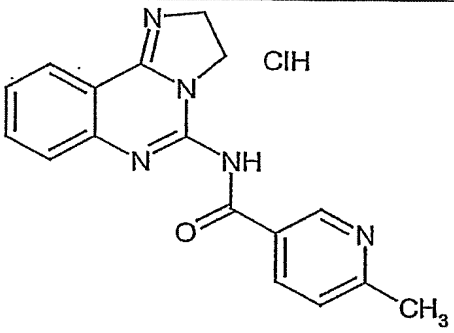
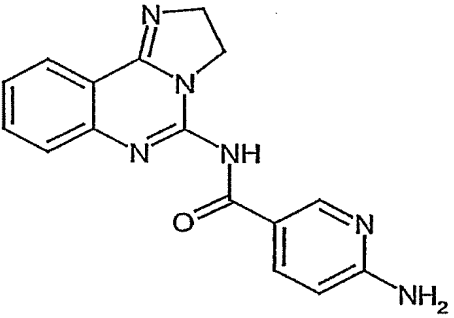
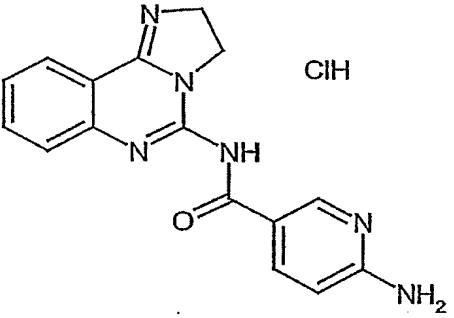
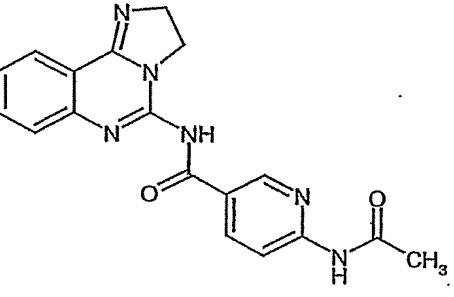
- 149 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-142	 <chem>O=C(O)c1ccncc1NC2=NC3=CC=CC=C3N4CCN=C42</chem>	335,32	336	358-359	B
2-143	 <chem>CS(=O)(=O)Nc1ccncc1NC2=NC3=CC=CC=C3N4CCN=C42</chem>	384,42	385	265-269	A
2-144	 <chem>Nc1ccncc1NC2=NC3=CC=CC=C3N4CCN=C42</chem>	306,33	307	263-266	A

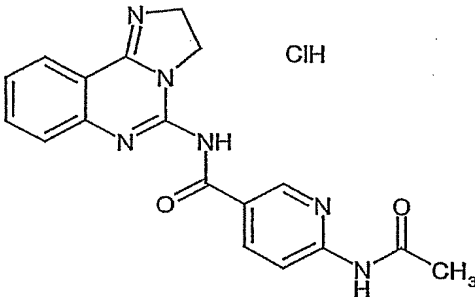
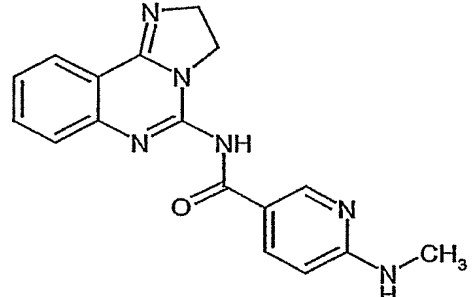
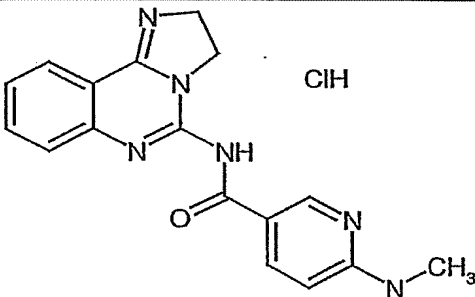
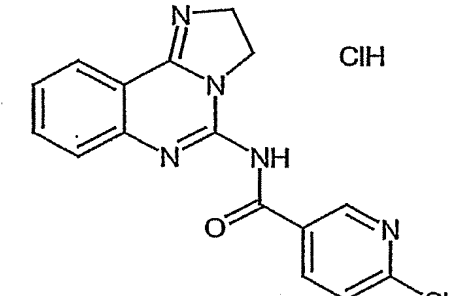
- 150 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-145		420,35	307	229(dec.)	B
2-146		361,41	362	219(dec.)	B
2-147		305,34	306	195 - 196	A

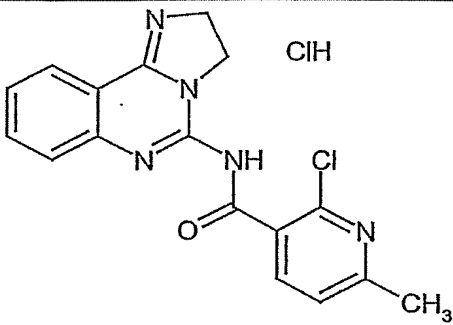
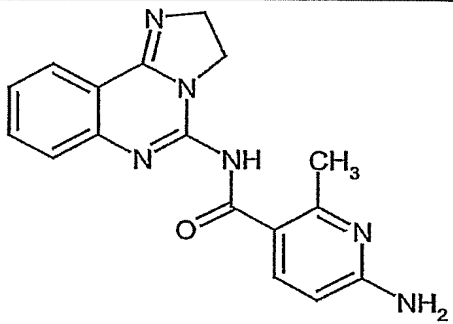
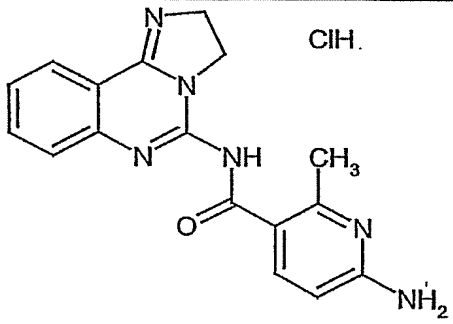
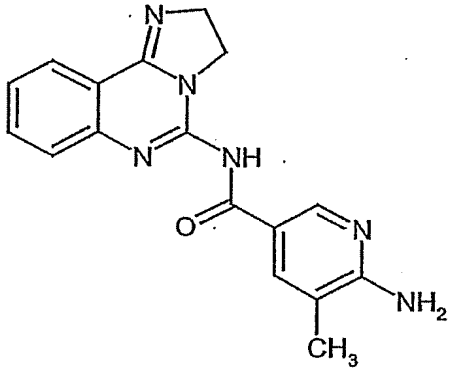
- 151 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-148	 <chem>Cc1ccncc1NC(=O)c2nc3c(nc2)ccccc3N</chem> ClH	341,80	306	310 (dec.)	A
2-149	 <chem>Nc1ccncc1NC(=O)c2nc3c(nc2)ccccc3N</chem>	306,33	307	> 300	A
2-150	 <chem>Nc1ccncc1NC(=O)c2nc3c(nc2)ccccc3N</chem> ClH	342,79	307	290 (dec.)	A
2-151	 <chem>CC(=O)Nc1ccc(NC(=O)c2nc3c(nc2)ccccc3N)cc1NC(=O)c4ccncc4</chem>	348,37	349	320 (dec.)	A

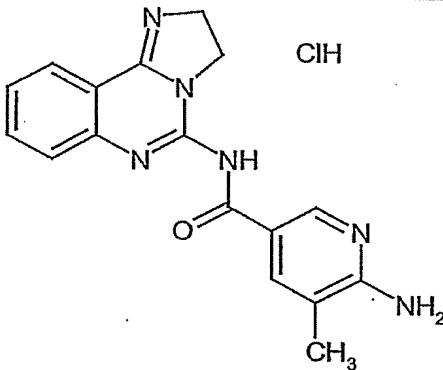
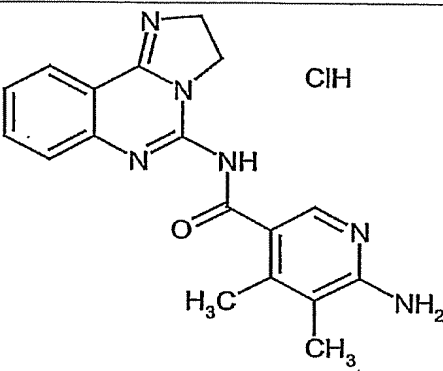
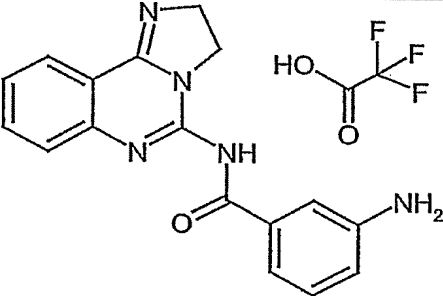
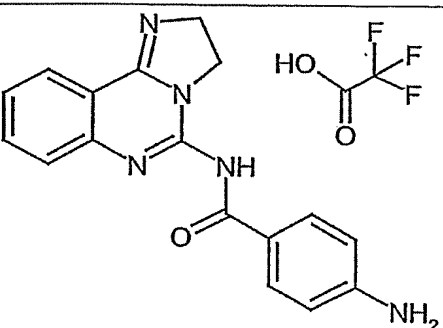
- 152 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-152	 ClH	384,83	349	312 (dec.)	A
2-153		320,36	320	196-197	B
2-154	 ClH	356,82	320	300(dec.)	B
2-155	 ClH	362,22	326	324 (dec.)	B

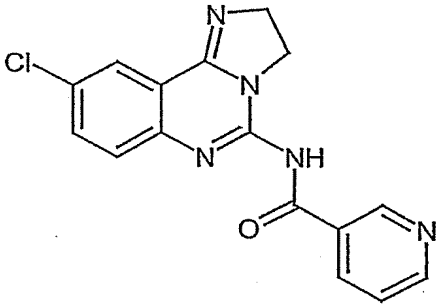
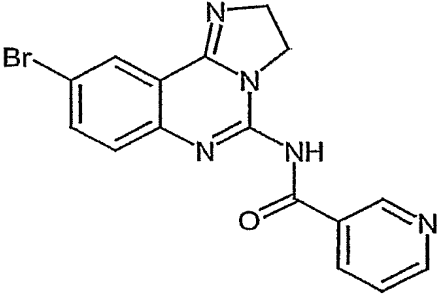
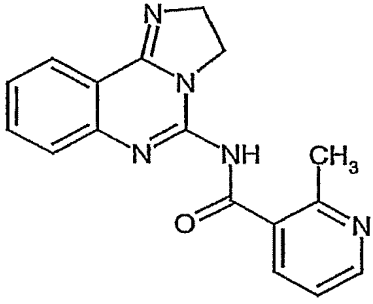
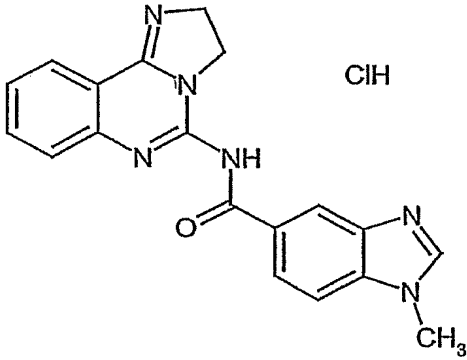
- 153 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-156	 <chem>Cc1cc(Cl)cc(NC(=O)N2C=NC3=CC=CC=C3N2C4=CC=CC=C4)cc1.Cl</chem>	376,25	340	287 (dec.)	B
2-157	 <chem>Cc1cc(N)cc(NC(=O)N2C=NC3=CC=CC=C3N2C4=CC=CC=C4)cc1</chem>	320,36	321	146-148	B
2-158	 <chem>Cc1cc(N)cc(NC(=O)N2C=NC3=CC=CC=C3N2C4=CC=CC=C4)cc1.Cl</chem>	356,82	321	289(dec.)	B
2-159	 <chem>Cc1cc(N)cc(NC(=O)N2C=NC3=CC=CC=C3N2C4=CC=CC=C4)cc1</chem>	320,36	320	246-247	B

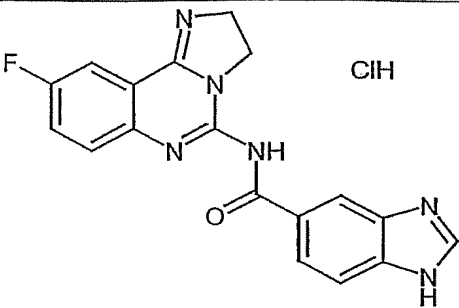
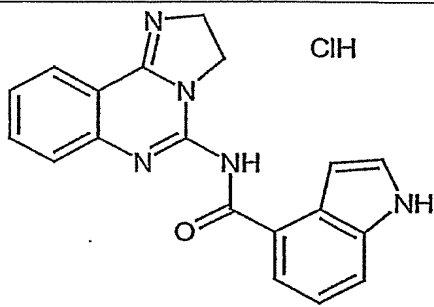
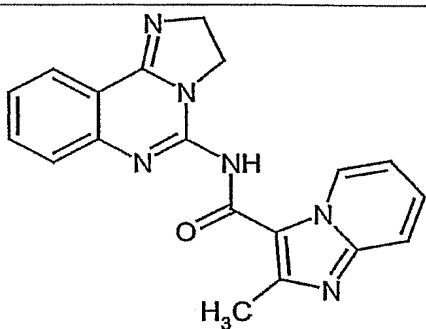
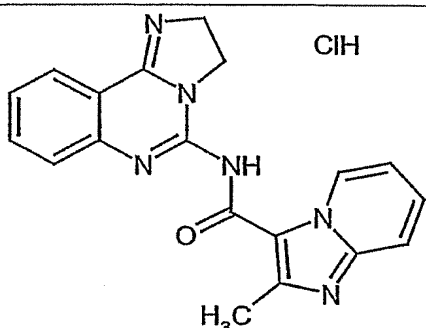
- 154 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-160	 ClH	356,82	320	311(dec.)	B
2-161	 ClH	370,84	334	298(dec.)	B
2-162	 HO-CF ₃	419,37	306	191(dec.)	B
2-163	 HO-CF ₃	419,37	306	232(dec.)	B

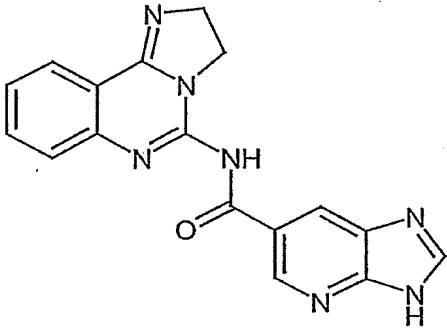
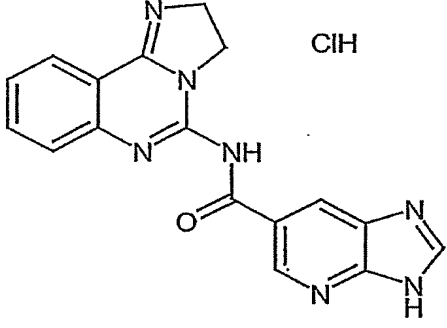
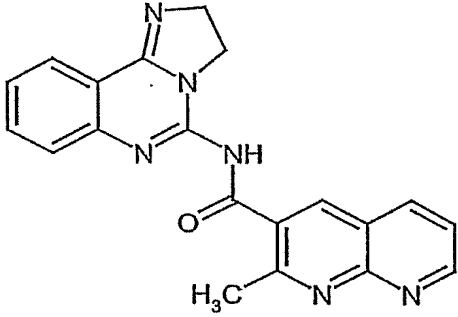
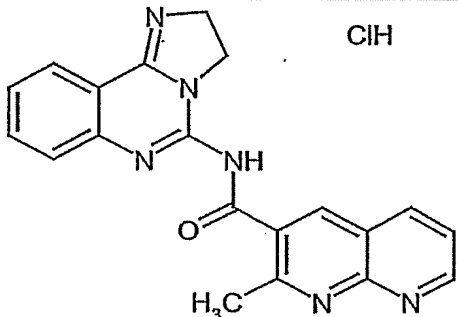
- 155 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-164		461,40	348	247(dec.)	A
2-165		328,76	292	291(dec.)	B
2-166		444,38	331	221(dec.)	A
2-167		380,84	345	333(dec.)	B

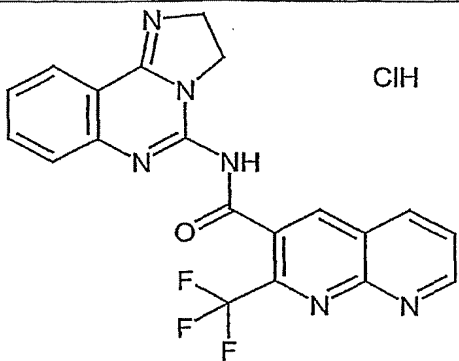
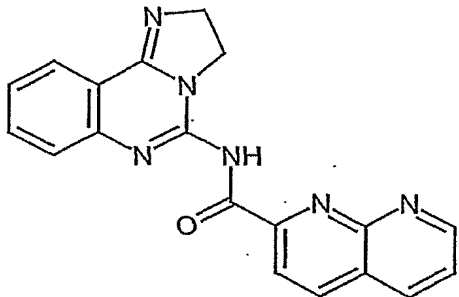
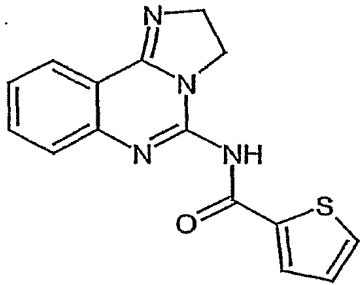
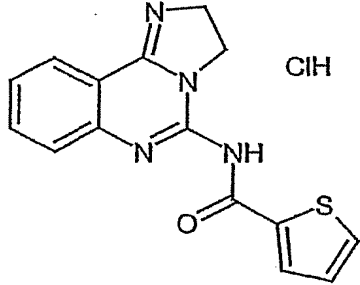
- 156 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-168	 ClH	329,36	330	160(dec.)	B
2-169	 ClH	365,83	330	295(dec.)	B
2-170	 ClH	344,38	345	277-279	B
2-171	 ClH	380,84	345	328(dec.)	B

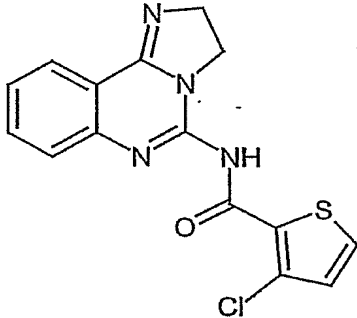
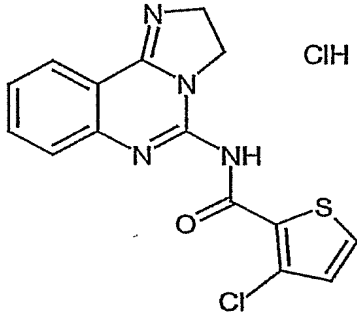
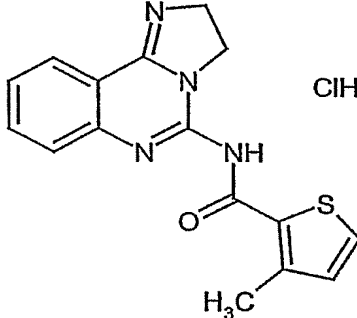
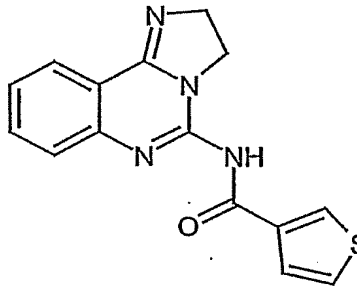
- 157 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-172		331,34	332	>300	A
2-173	 ClH	367,80	332	287(dec.)	A
2-174		356,39	356	296(dec.)	B
2-175	 ClH	392,85	356	270(dec.)	B

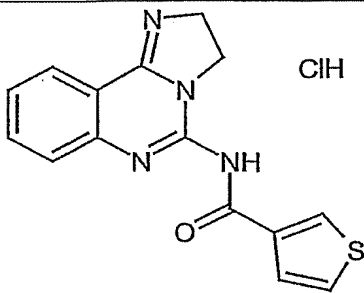
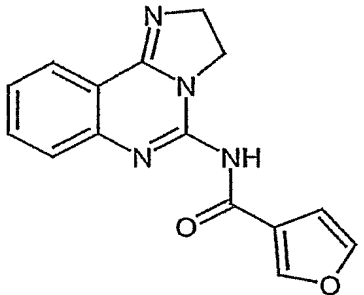
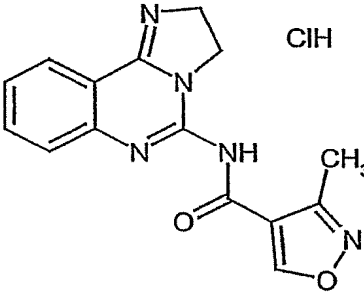
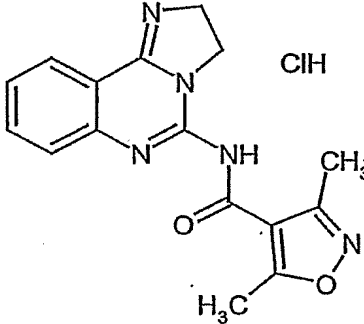
- 158 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-176	 ClH	446,82	410	248-249	B
2-177		342,36	342	275(dec.)	B
2-178		296,35	297	187 - 188	B
2-179	 ClH	332,81	297	310 (dec.)	A

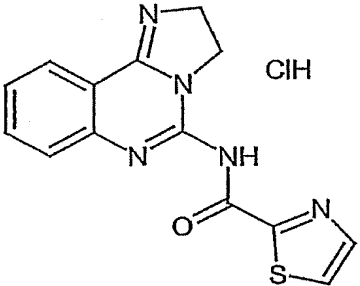
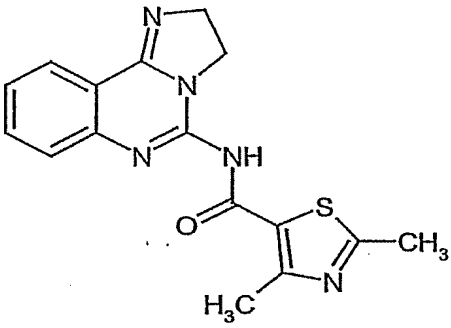
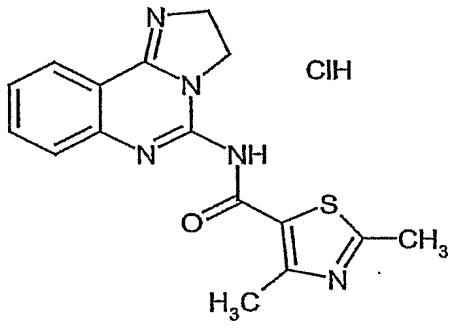
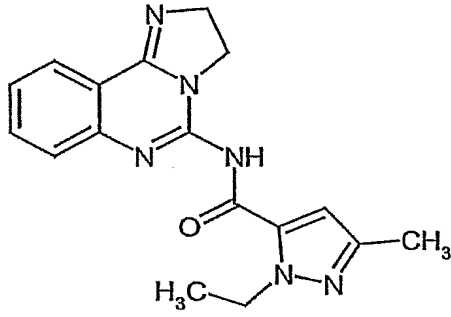
- 159 -

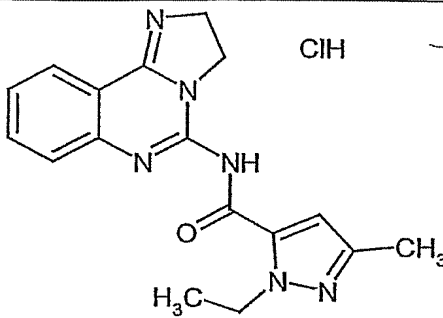
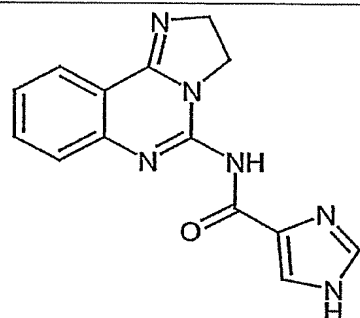
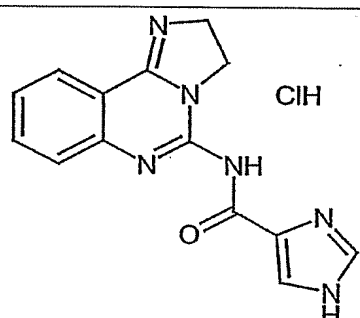
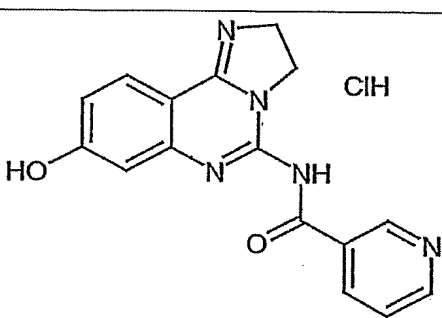
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-180	 <chem>Nc1nc2ccccc2n1C(=O)Nc3cc(Cl)cc3s</chem>	330,80	330	198-199	B
2-181	 <chem>Nc1nc2ccccc2n1C(=O)Nc3cc(Cl)cc3s.Cl</chem>	367,26	330	298(dec.)	B
2-182	 <chem>Cc1cc(NC(=O)Nc2nc3ccccc3n2)ccsc1.Cl</chem>	346,84	310	> 250	B
2-183	 <chem>Nc1nc2ccccc2n1C(=O)Nc3ccsc3</chem>	296,35	297	167 (dec.)	B

- 160 -

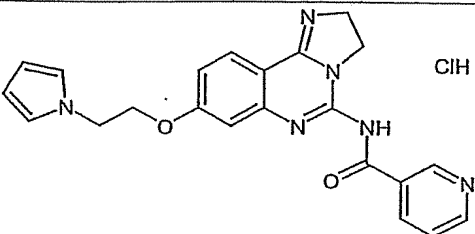
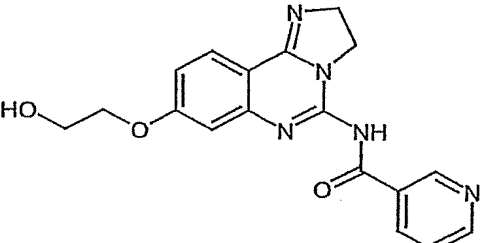
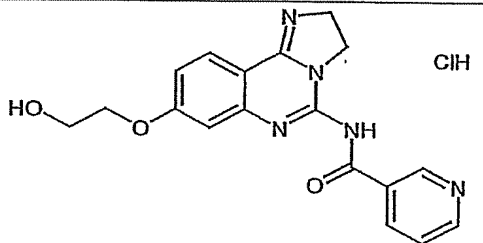
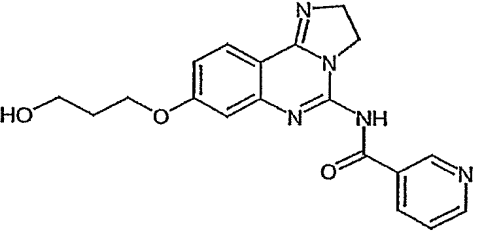
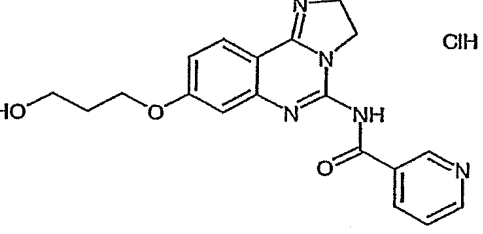
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-184	 ClH	332,81	297	297 (dec.)	B
2-185		280,29	280	217-218	B
2-186	 ClH	331,76	295	285(dec.)	B
2-187	 ClH	345,79	309	280-281	B

- 161 -

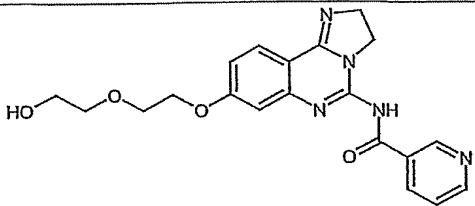
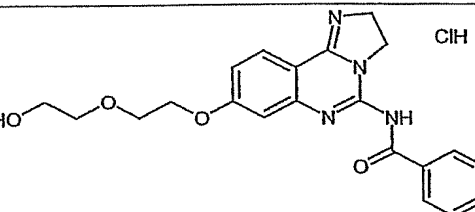
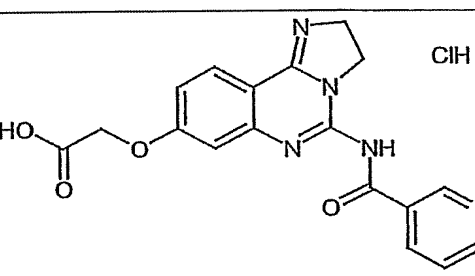
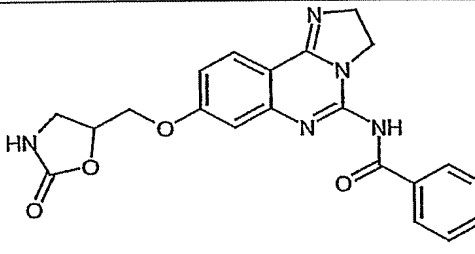
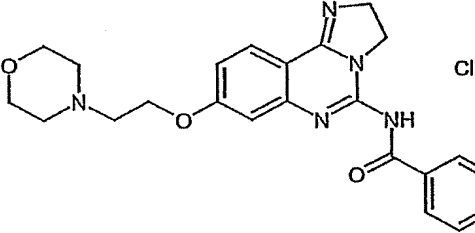
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-188	 <chem>C1=CN=C(NC(=O)c2cc[nH]2)c3nc4ccccc4n3C1</chem> ClH	333,80	298	306(dec.)	B
2-189	 <chem>Cc1nc(C)c(C(=O)Nc2nc3ccccc3n2)s1</chem>	325,39	326	243 (dec.)	B
2-190	 <chem>Cc1nc(C)c(C(=O)Nc2nc3ccccc3n2)s1</chem> ClH	361,86	326	289 - 290	A
2-191	 <chem>Cc1nn(C)c(C(=O)Nc2nc3ccccc3n2)c1</chem>	322,37	322	207-208	B

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-192	 ClH	358,83	322	271-272	B
2-193		280,29	281	265 (dec.)	B
2-194	 ClH	316,75	281	309 - 310	B
2-195	 ClH	343,78	308	270-274(dec.)	B

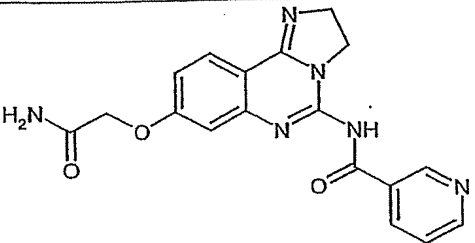
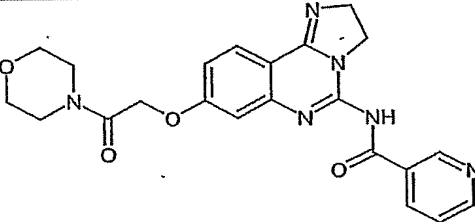
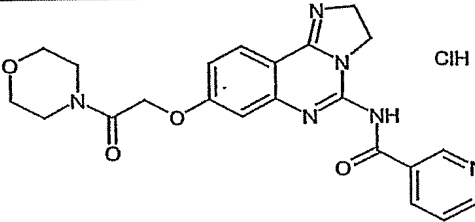
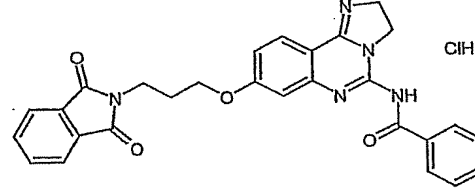
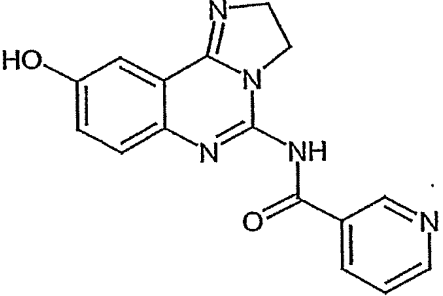
- 163 -

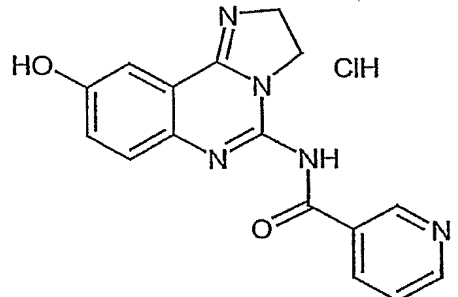
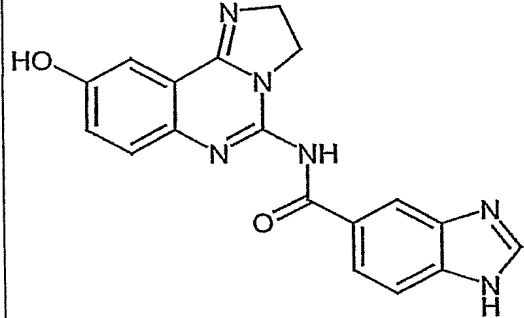
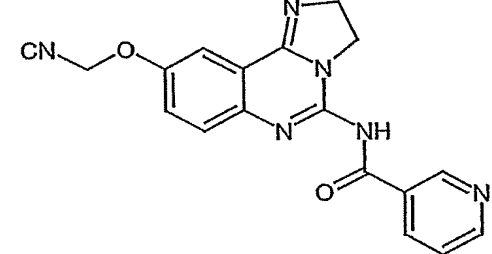
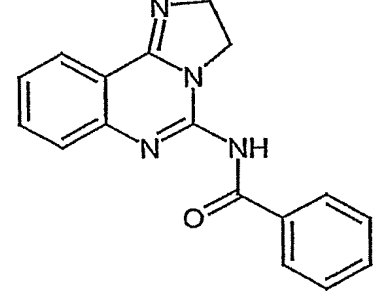
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-196	 ClH	436,90	401	239	B
2-197		351,37	352	210-215(dec.)	B
2-198	 ClH	387,83	352	249(dec.)	B
2-199		365,39	366	127	A
2-200	 ClH	401,86	366	243(dec.)	B

- 164 -

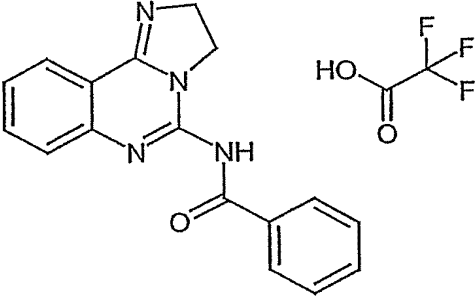
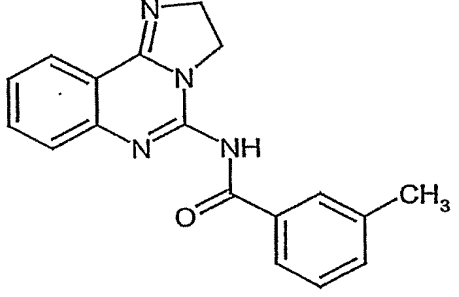
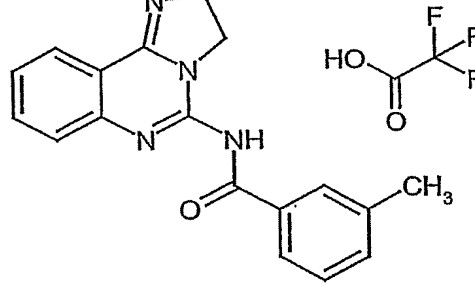
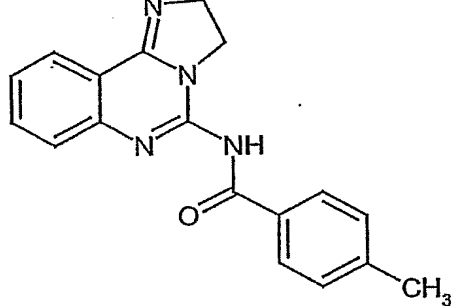
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-201		395,42	396	181	B
2-202		431,88	396	229(dec.)	B
2-203		401,81	366	231(dec.)	B
2-204		406,40	407	265-269(dec.)	B
2-205		456,94	421	243-247(dec.)	B

- 165 -

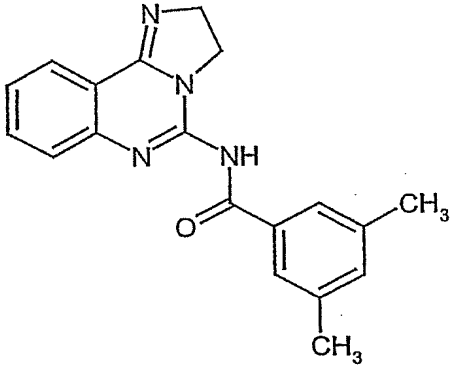
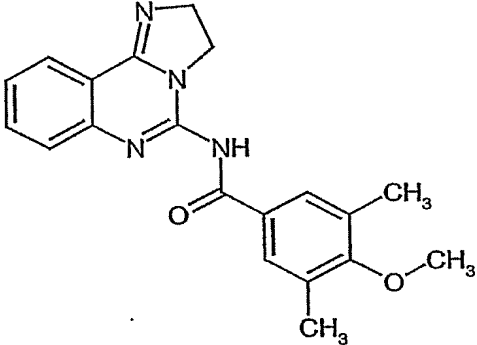
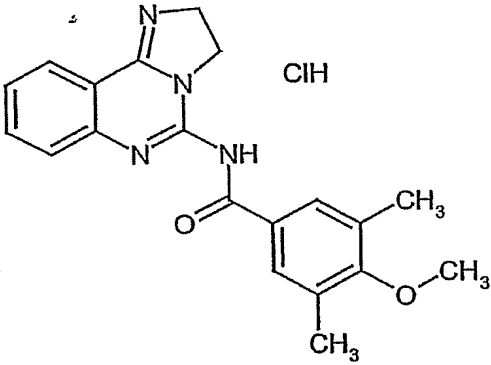
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-206		364,37	365	296	B
2-207		434,46	435	232-236(dec.)	B
2-208		470,92	435	227	B
2-209		530,98	495	247	A
2-210		307,31	308	>300	B

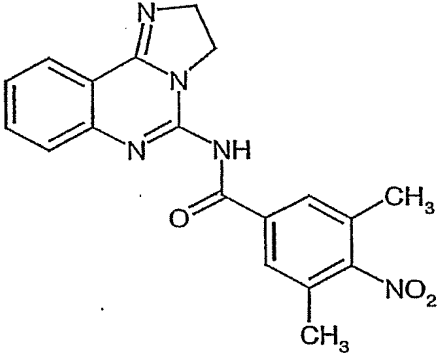
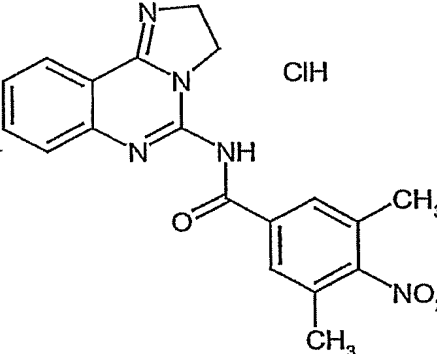
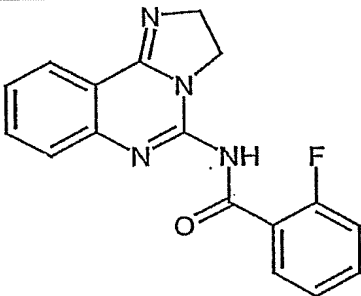
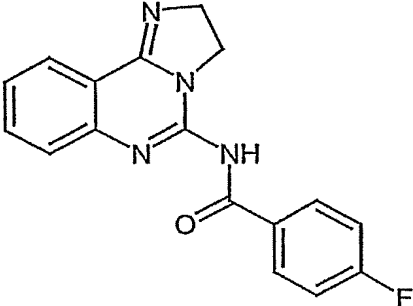
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-211		343,78	308	>300	A
2-212		346,35	347	296(dec.)	B
2-213		346,35	347	209	B
2-214		290,33	291	201-203(dec.)	C

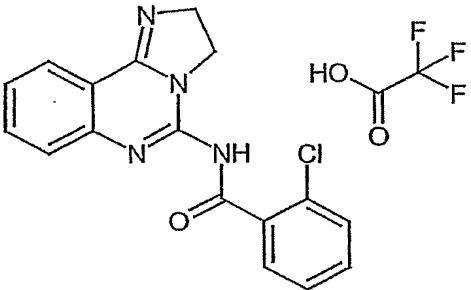
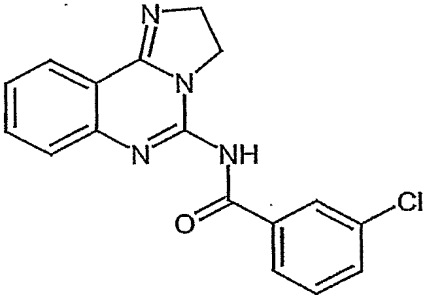
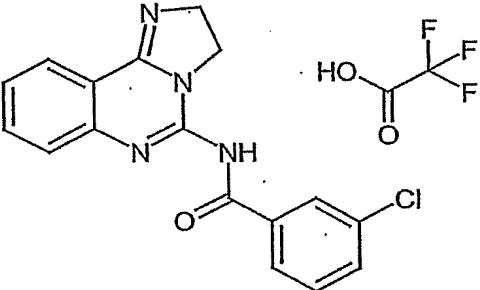
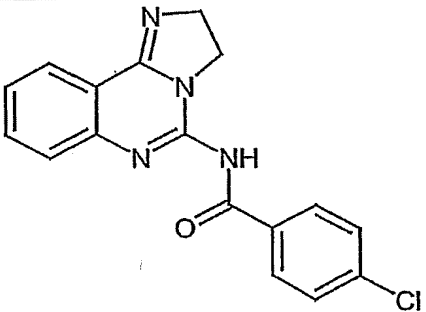
- 167 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-215		404,35	291	238-242	B
2-216		304,35	305	201-203	D
2-217		418,38	305	239-241	B
2-218		304,35	305	185-186	D

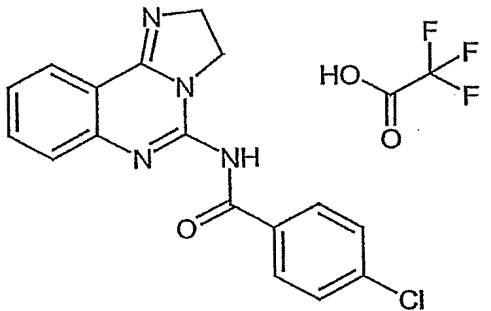
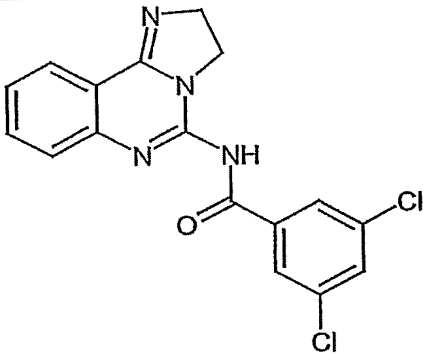
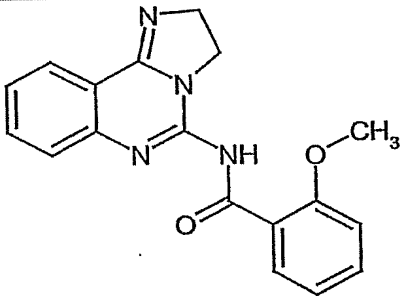
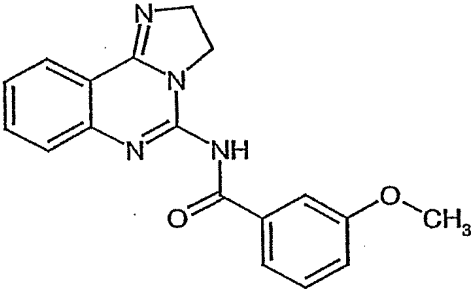
- 168 -

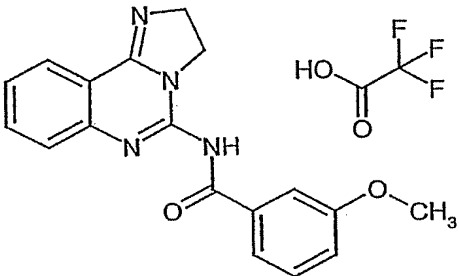
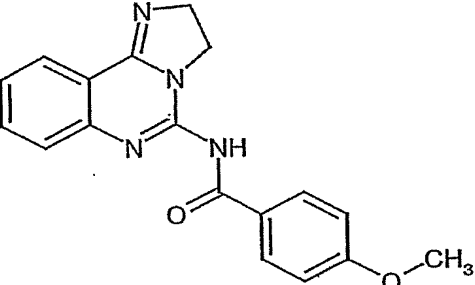
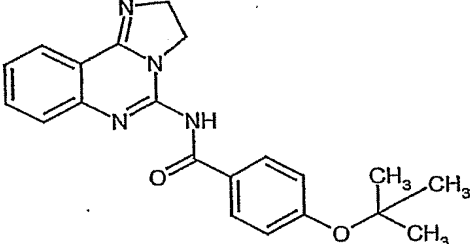
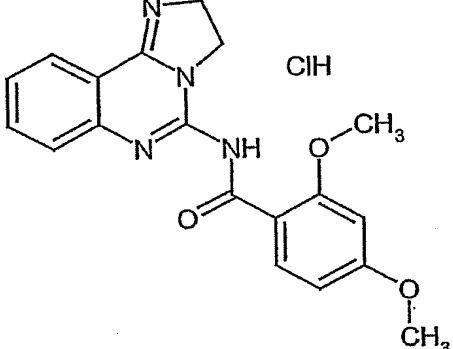
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-219		318,38	319	246-248	D
2-220		348,41	349	216-218	D
2-221	 ClH	384,87	349	288 (dec.)	D

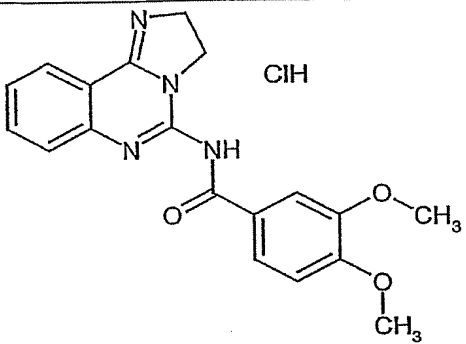
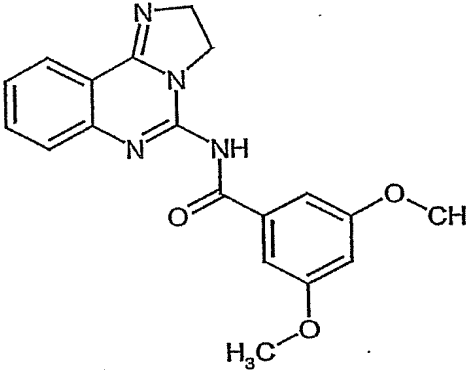
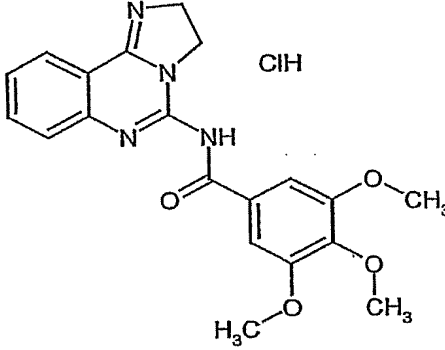
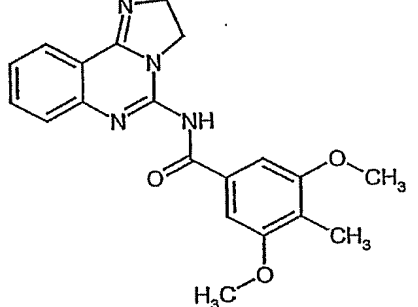
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-222		363,38	364	277 (dec.)	D
2-223		399,84	364	313 (dec.)	D
2-224		308,32	309	202-204	C
2-225		308,32	309	210-212	D

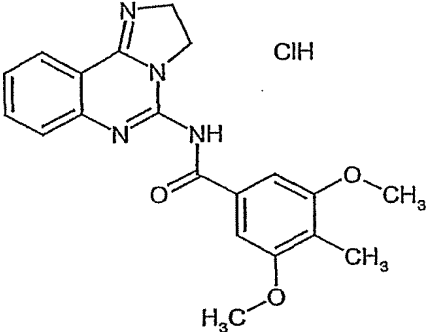
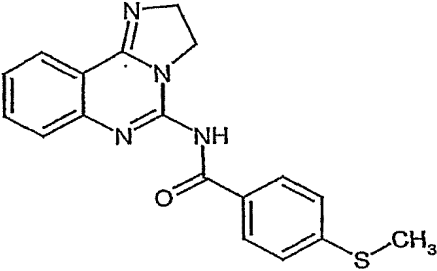
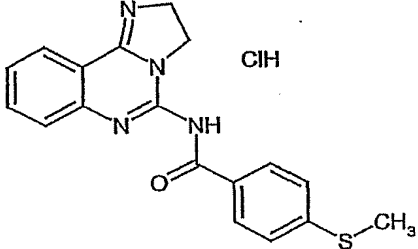
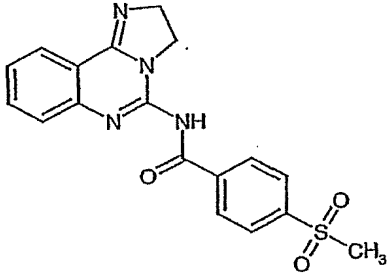
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-226		438,80	325	221-224	D
2-227		324,77	325	196-197	D
2-228		438,80	325	233-235	C
2-229		324,77	325	226-228	D

- 171 -

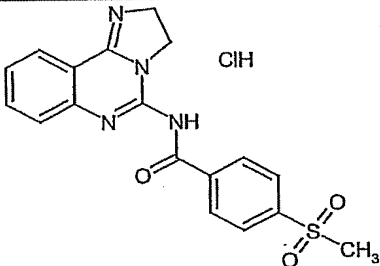
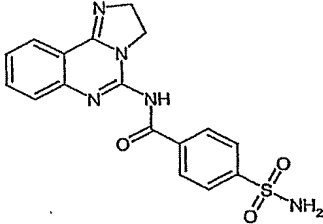
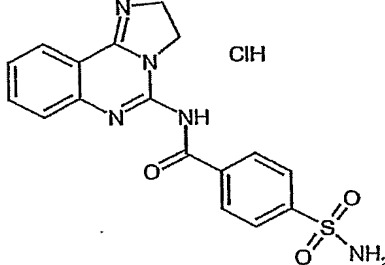
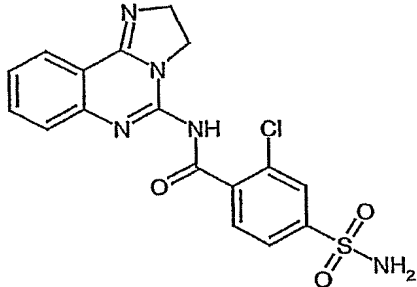
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-230		438,80	325	243-245	D
2-231		359,22	358	268-269	D
2-232		320,35	321	185-187	D
2-233		320,35	321	202-204	D

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-234		434,38	321	209-211	C
2-235		320,35	321	300 (dec.)	D
2-236		362,44	363	>410	D
2-237		386,84	351	259 (dec.)	D

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-238	 ClH	386,84	351	274 (dec.)	B
2-239		350,38	351	330 (dec.)	D
2-240	 ClH	416,87	381	291 (dec.)	D
2-241		364,41	365	248 (dec.)	D

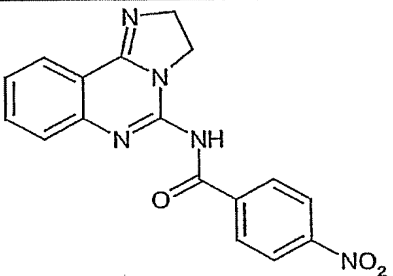
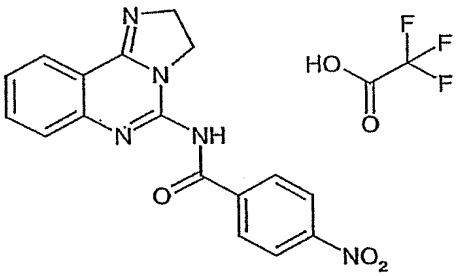
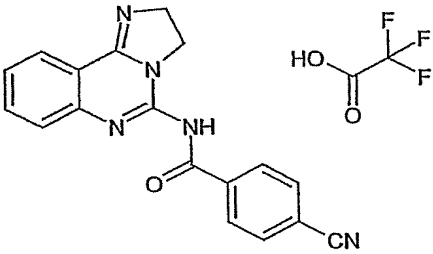
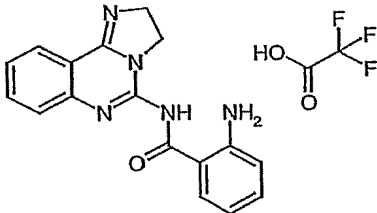
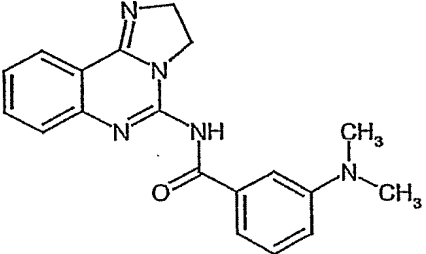
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-242	 ClH	400,87	365	321 (dec.)	D
2-243		336,42	337	169-170	D
2-244	 ClH	372,88	337	292 (dec.)	D
2-245		368,42	369	278 (dec.)	D

- 175 -

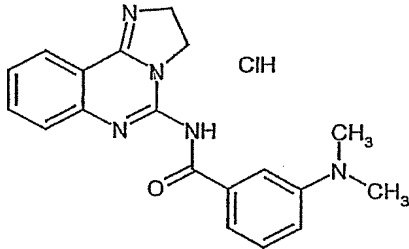
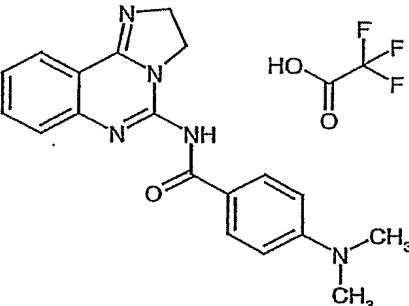
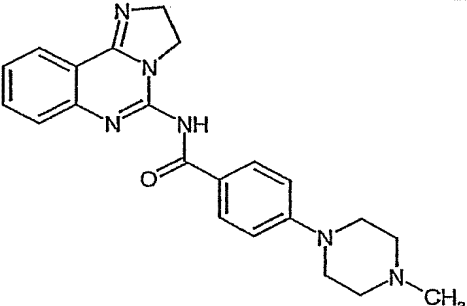
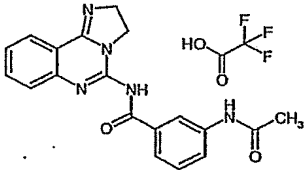
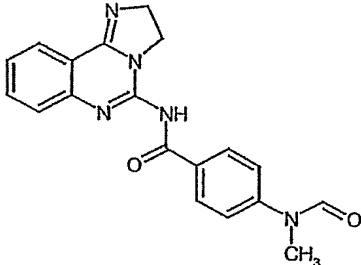
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-246	 <chem>Cs(=O)(=O)c1ccc(cc1)NC(=O)c2nc3c(nc2)C=C3</chem> ClH	404,88	369	320 (dec.)	D
2-247	 <chem>NS(=O)(=O)c1ccc(cc1)NC(=O)c2nc3c(nc2)C=C3</chem>	369,40	370	278 (dec.)	C
2-248	 <chem>NS(=O)(=O)c1ccc(cc1)NC(=O)c2nc3c(nc2)C=C3</chem> ClH	405,87	370	308 (dec.)	C
2-249	 <chem>NS(=O)(=O)c1ccc(Cl)cc1NC(=O)c2nc3c(nc2)C=C3</chem>	403,85	403	240 (dec.)	D

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-250	<p>ClH</p>	440,31	403	300 (dec.)	D
2-251	<p>HO-C(=O)-C(F)(F)F</p>	449,35	336	198-200	D
2-252		335,32	334	265-267	D
2-253	<p>HO-C(=O)-C(F)(F)F</p>	449,35	336	238-239	D

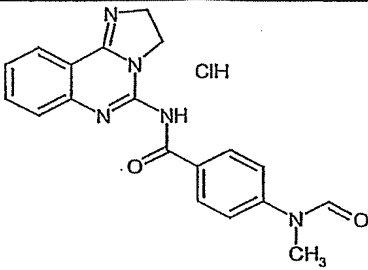
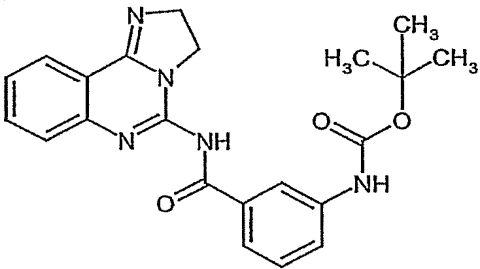
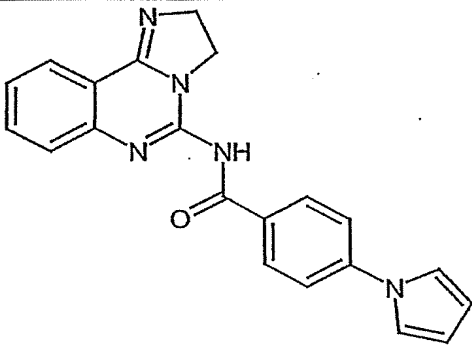
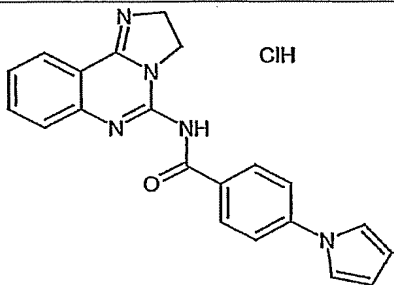
- 177 -

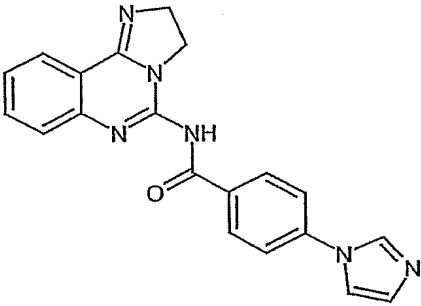
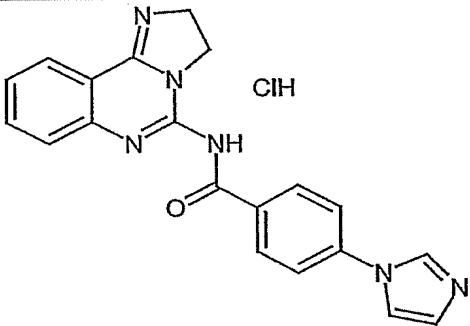
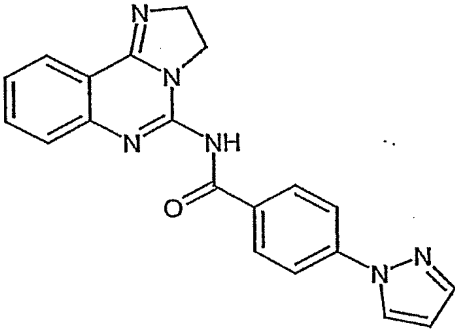
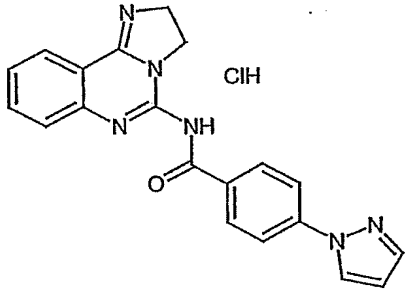
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-254		335,32	334	279-281	D
2-255		449,35	336	265 (dec.)	D
2-256		429,36	316	248-250	D
2-257		419,37	306	175 (dec.)	D
2-258		333,40	334	188-190	D

- 178 -

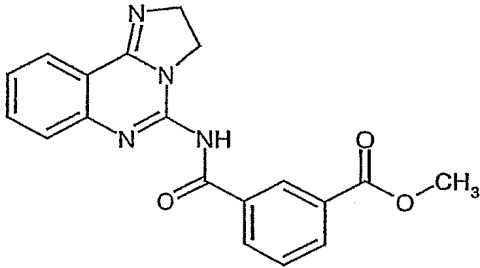
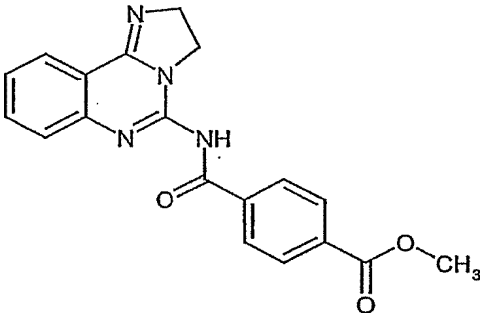
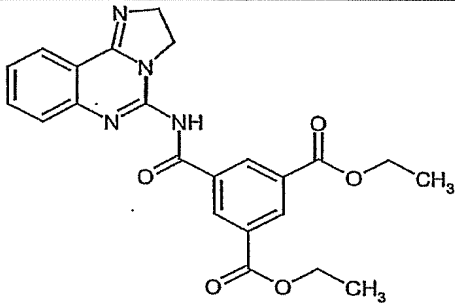
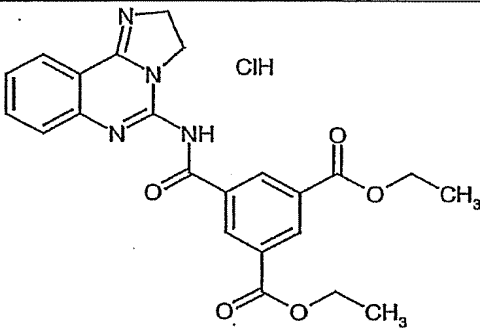
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-259	 ClH	369,86	334	266 (dec.)	D
2-260	 HO-CF ₃	447,42	334	240 (dec.)	D
2-261		388,48	389	218-222	D
2-262	 HO-CF ₃	461,40	348	253(dec.)	D
2-263		347,38	348	208-210	D

- 179 -

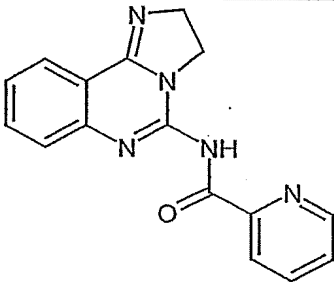
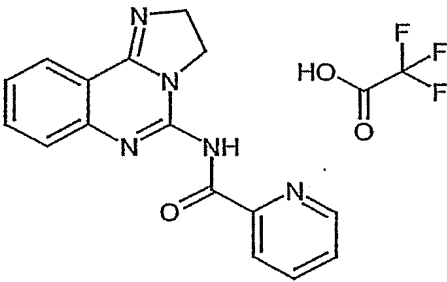
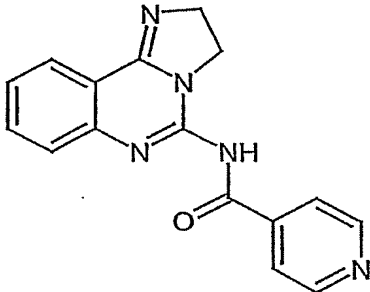
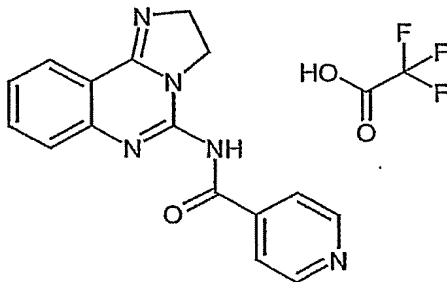
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-264	 <chem>CN(C)C(=O)c1ccc(NC(=O)c2nc3ccccc3n2)n1</chem> ClH	383,84	348	304 (dec.)	D
2-265	 <chem>CC(C)(C)OC(=O)Nc1ccc(NC(=O)c2nc3ccccc3n2)n1</chem>	405,46	406	280 (dec.)	D
2-266	 <chem>C1CCN1c2ccc(NC(=O)c3nc4ccccc4n3)n2</chem>	355,40	356	218-220	D
2-267	 <chem>C1CCN1c2ccc(NC(=O)c3nc4ccccc4n3)n2</chem> ClH	391,86	356	309 (dec.)	D

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-268		356,39	357	267 (dec.)	D
2-269		392,85	357	324(dec.)	D
2-270		356,39	357	209-211	D
2-271		392,85	357	319 (dec.)	D

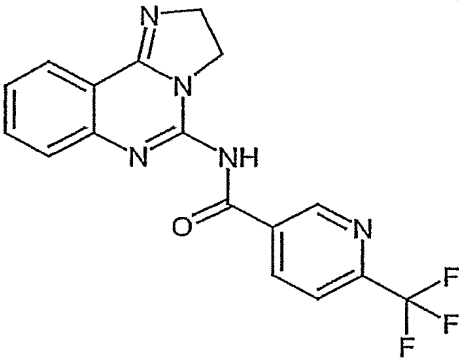
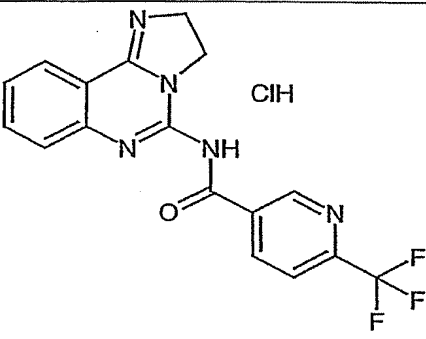
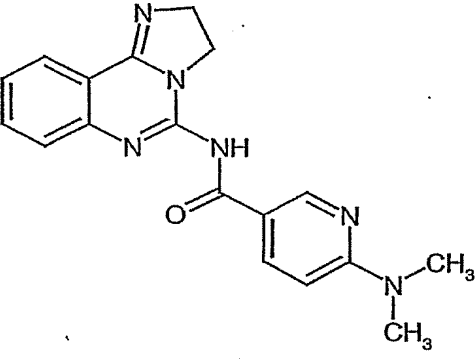
- 181 -

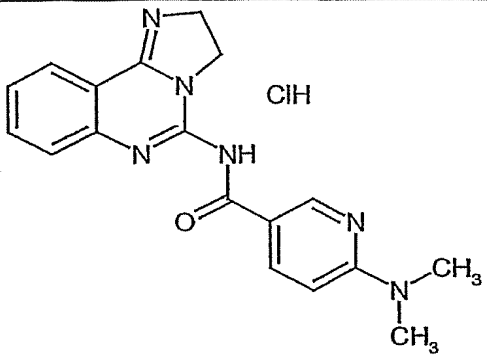
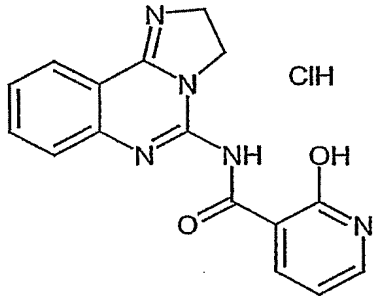
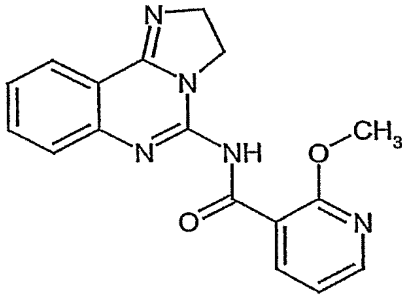
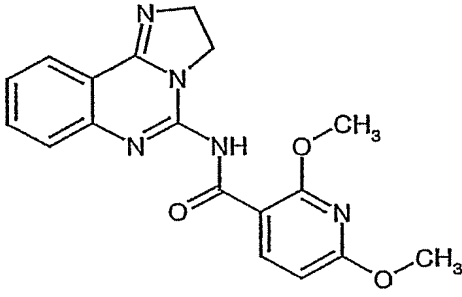
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-272		348,36	349	224-226	D
2-273		348,36	349	253-255	D
2-274		434,46	435	289 (dec.)	D
2-275		470,92	435	282	D

- 182 -

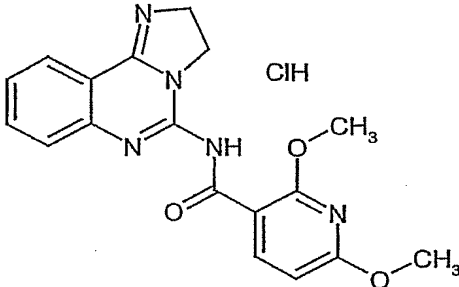
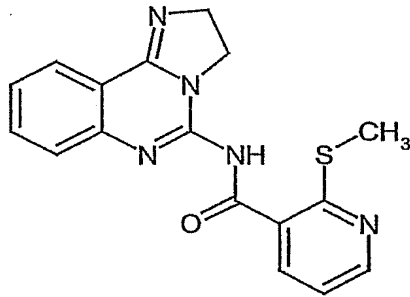
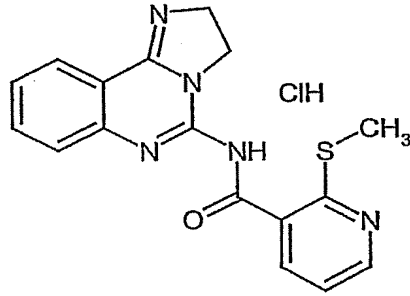
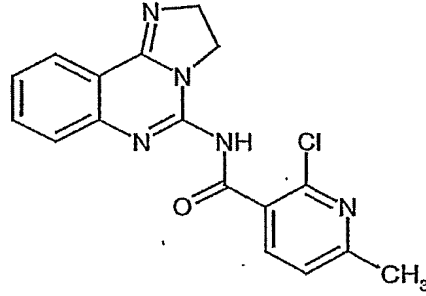
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-276		291,31	292	204 - 205	C
2-277		405,34	292	206 (dec.)	C
2-278		291,31	292	224 - 225	C
2-279		405,34	292	2310(dec.)	C

- 183 -

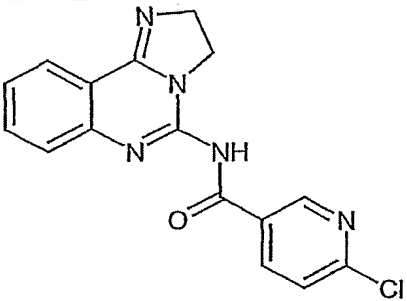
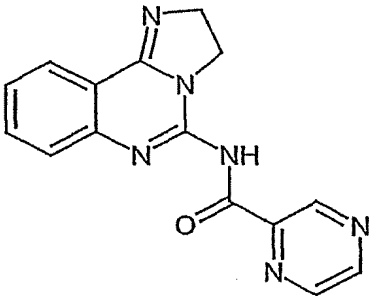
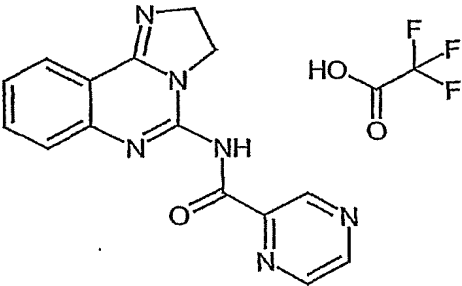
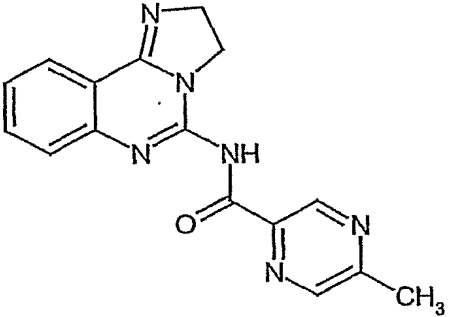
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-280		359,31	360	219 - 220	D
2-281		395,77	360	> 250	C
2-282		334,38	335	249 (dec.)	D

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-283	 <chem>CN(C)c1ccncc1C(=O)Nc2nc3c(nc2)CCN3</chem> ClH	370,84	335	311 (dec.)	C
2-284	 <chem>Oc1ccncc1C(=O)Nc2nc3c(nc2)CCN3</chem> ClH	343,78	308	346 (dec.)	D
2-285	 <chem>COC1=CC=CC=C1C(=O)Nc2nc3c(nc2)CCN3</chem>	321,34	322	198 - 199	C
2-286	 <chem>COC1=CC(OC)=CC=C1C(=O)Nc2nc3c(nc2)CCN3</chem>	351,37	352	244 - 245	D

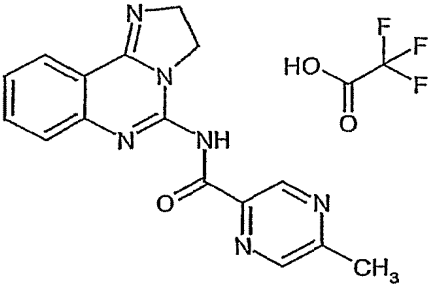
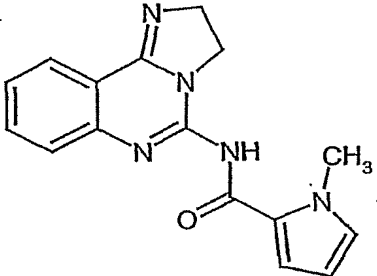
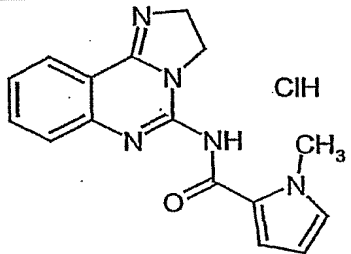
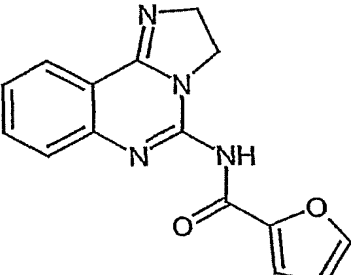
- 185 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-287	 <chem>COC1=CC=C(C(=O)NC2=NC3=CC=CC=C3N4C=NC5=CC=CC=C5N4C2)C=C1OC</chem> ClH	387,83	352	210 (dec.)	C
2-288	 <chem>CSC1=CC=C(C(=O)NC2=NC3=CC=CC=C3N4C=NC5=CC=CC=C5N4C2)C=C1</chem>	337,41	338	233 - 234	D
2-289	 <chem>CSC1=CC=C(C(=O)NC2=NC3=CC=CC=C3N4C=NC5=CC=CC=C5N4C2)C=C1</chem> ClH	373,87	338	298 - 299	C
2-290	 <chem>Cc1cc(Cl)cc(C(=O)NC2=NC3=CC=CC=C3N4C=NC5=CC=CC=C5N4C2)c1</chem>	339,79	340	213 - 214	B

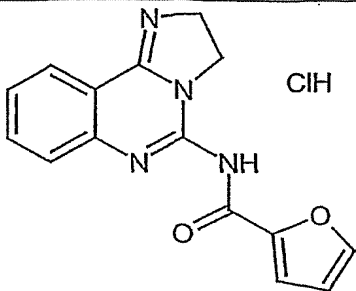
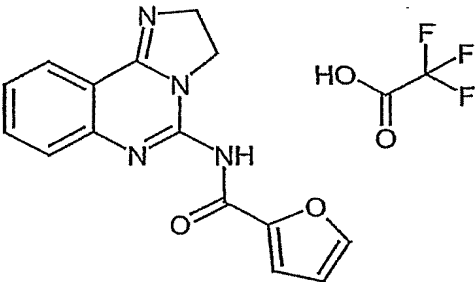
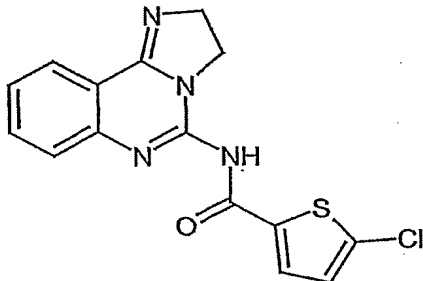
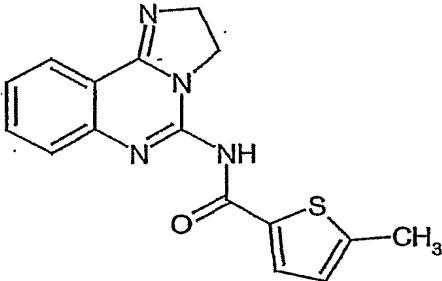
- 186 -

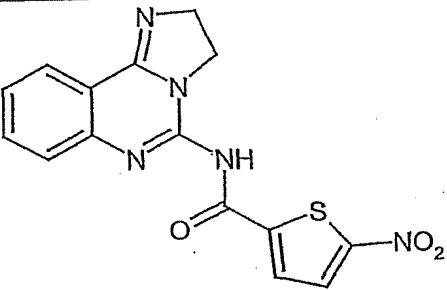
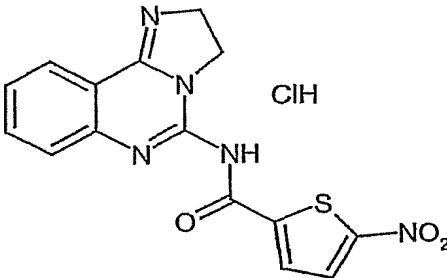
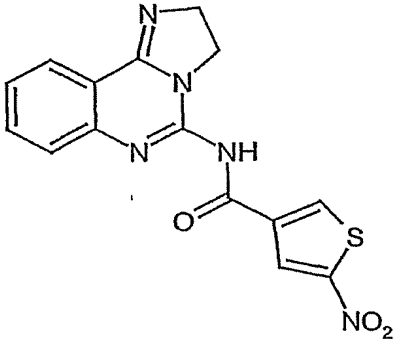
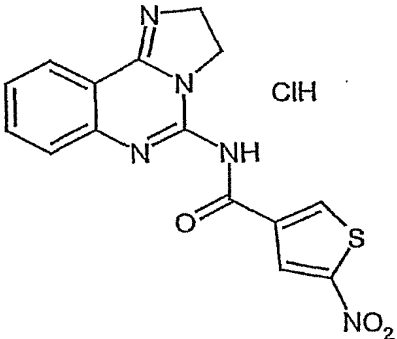
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-291		325,76	326	246 - 247	B
2-292		292,30	293	267 - 268	C
2-293		406,33	293	234 (dec.)	C
2-294		306,33	307	257 (dec.)	C

- 187 -

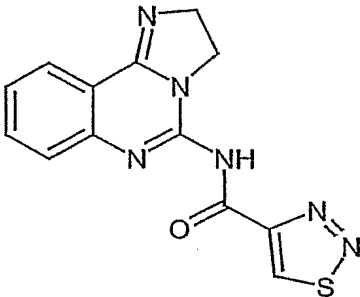
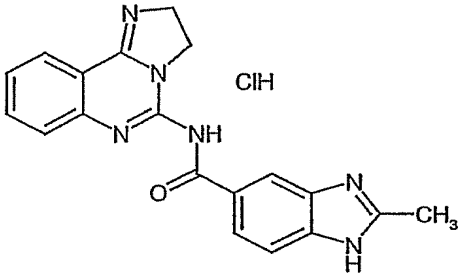
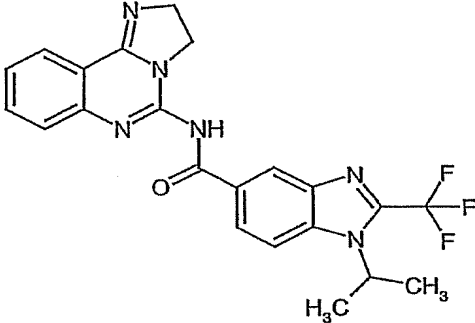
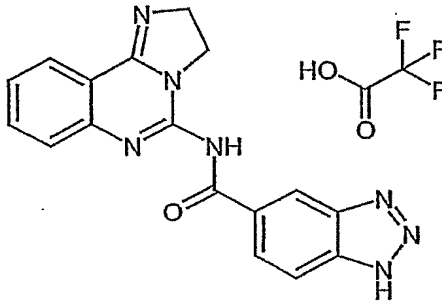
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-295		420,35	307	231 (dec.)	C
2-296		293,33	294	128 - 129	C
2-297		329,79	294	264 (dec.)	C
2-298		280,29	281	350 (dec.)	C

- 188 -

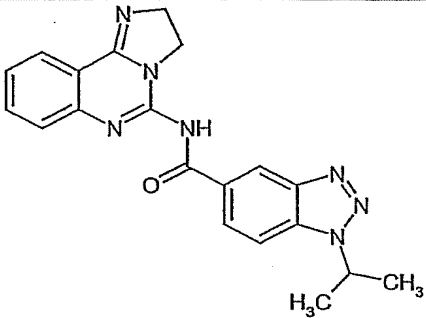
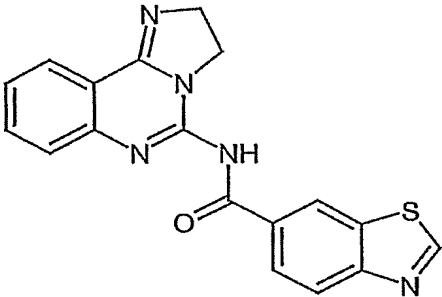
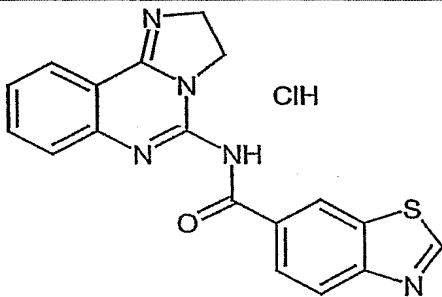
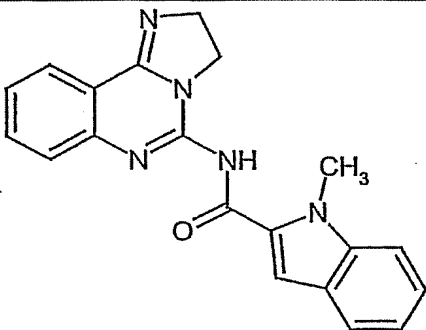
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-299		316,75	281	311 (dec.)	C
2-300		394,31	281	230-232	B
2-301		330,80	331	198 (dec.)	D
2-302		310,38	311	192 - 193	C

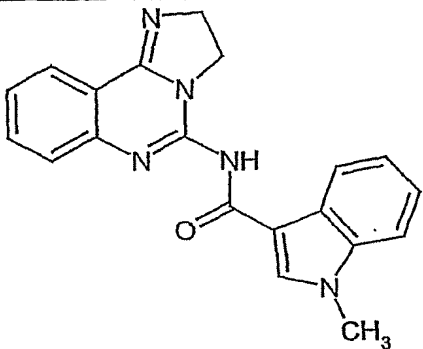
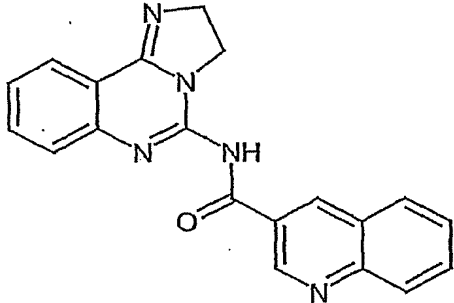
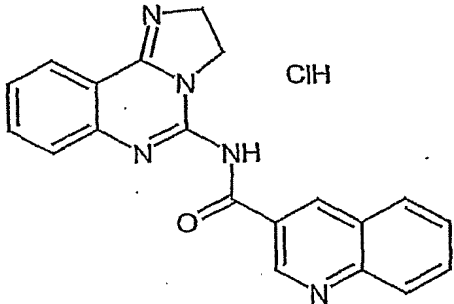
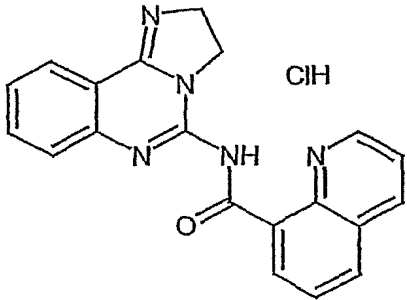
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-303		341,35	342	286 - 287	D
2-304		377,81	342	300 (dec.)	D
2-305		341,35	342	269 - 270	D
2-306		377,81	342	296 (dec.).	D

- 190 -

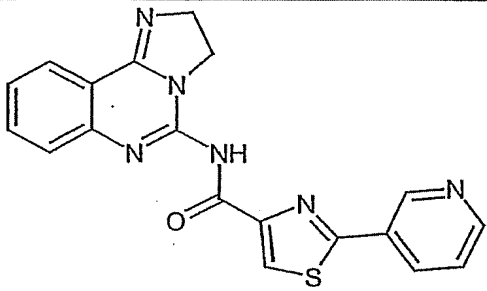
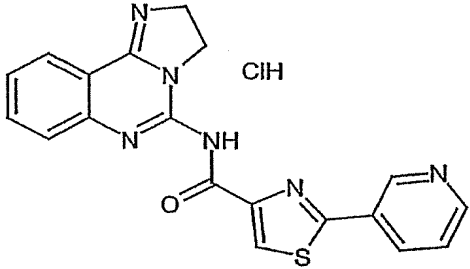
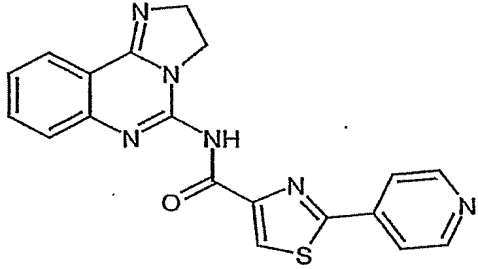
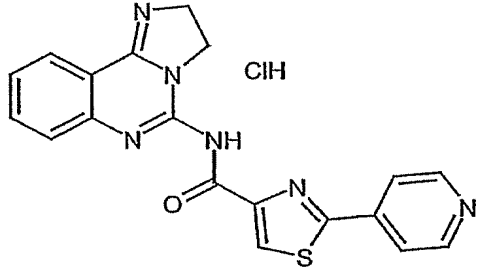
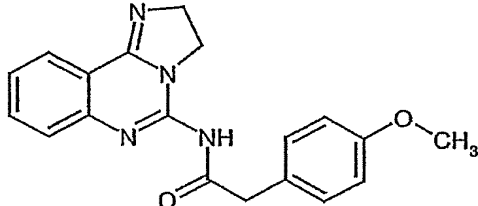
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-307		298,33	299	219 (dec.)	C
2-308		380,84	345	344 (dec.)	B
2-309		440,43	441	250-253	D
2-310		445,36	332	252 (dec.)	B

- 191 -

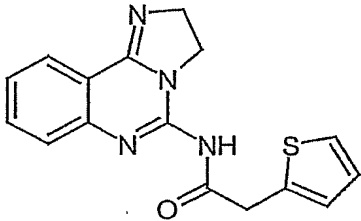
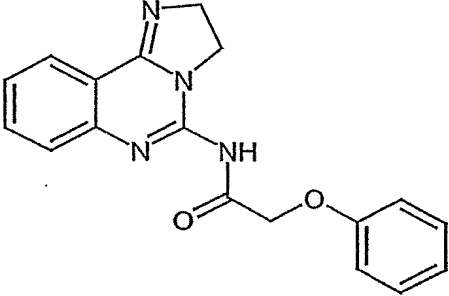
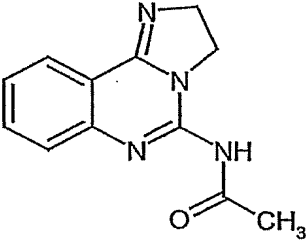
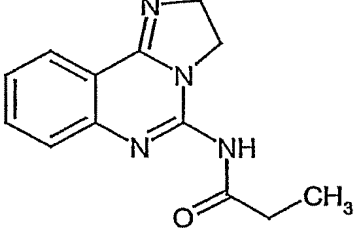
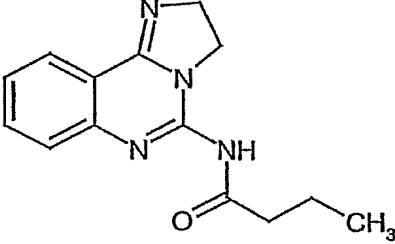
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-311	 <chem>CN1C=NC2=C(N1)C(=O)NC3=CC=CC=C3N2</chem>	373,42	374	202-203	D
2-312	 <chem>C1=NC2=CC=C(C=C2N1)C(=O)NC3=CC=C(C=C3)S4=NN=CS4</chem>	347,40	348	303-305	D
2-313	 <chem>C1=NC2=CC=C(C=C2N1)C(=O)NC3=CC=C(C=C3)S4=NN=CS4.Cl</chem>	383,86	348	314 (dec.)	C
2-314	 <chem>CN1C=CC2=CC=CC=C21C(=O)NC3=CC=CC=C3N4C=CC=CC=C4N5C=CC=CC=C5N4</chem>	343,39	344	259 - 260	D

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-315		343,39	344	288 - 289	D
2-316		341,38	342	263 - 264	D
2-317		377,84	342	319 (dec.)	B
2-318		377,84	342	316 (dec.)	D

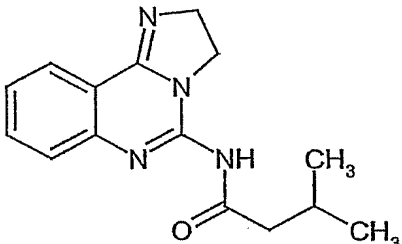
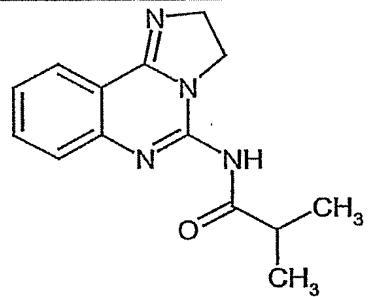
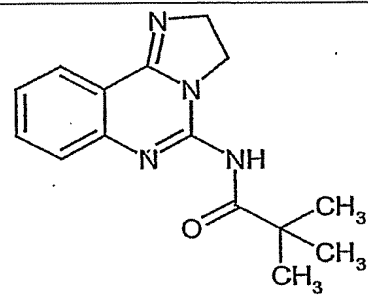
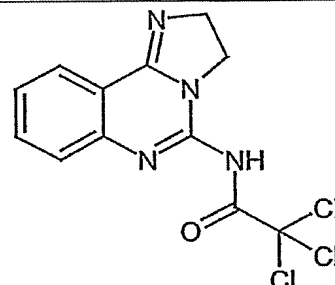
- 193 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-319		374,43	375	260 - 261	D
2-320		410,89	375	310 (dec.)	D
2-321		374,43	375	281 (dec.)	D
2-322		410,89	375	335 (dec.)	D
2-323		334,38	335	167 - 168	D

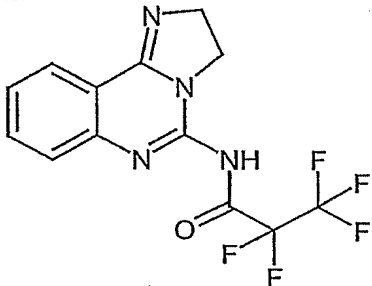
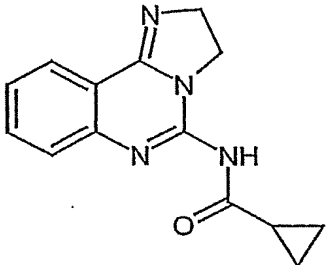
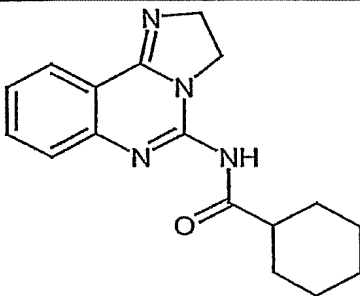
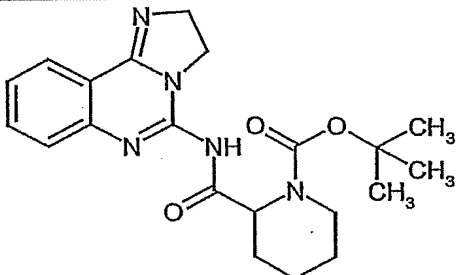
- 194 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-324		310,38	311	122 - 123	D
2-325		320,35	321	149 - 150	D
2-326		228,26	229	189	D
2-327		242,28	243	amorphous	D
2-328		256,31	257	121-122	D

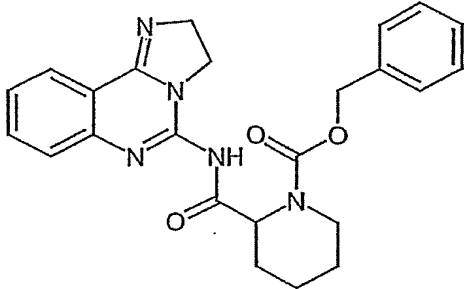
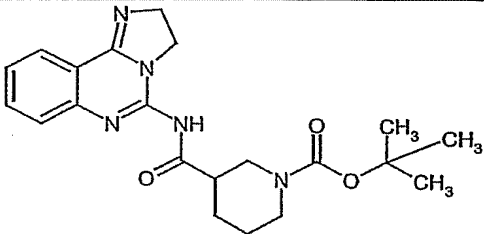
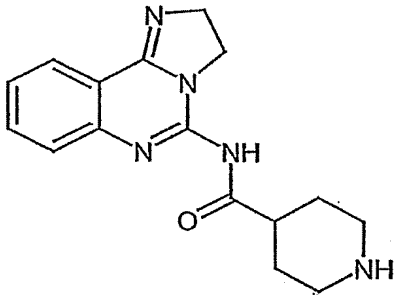
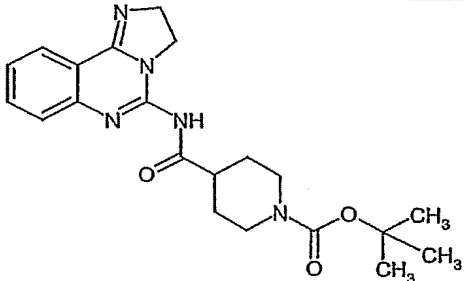
- 195 -

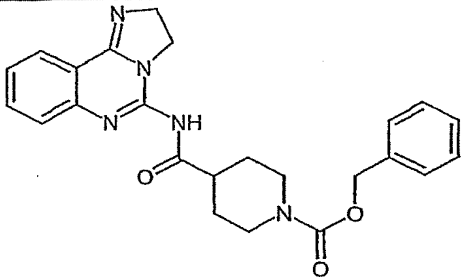
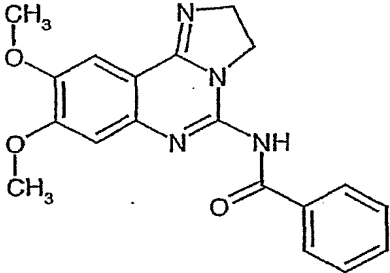
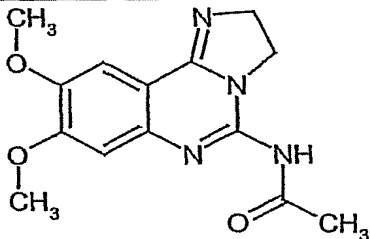
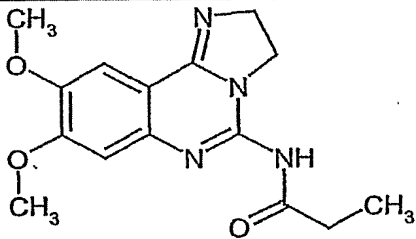
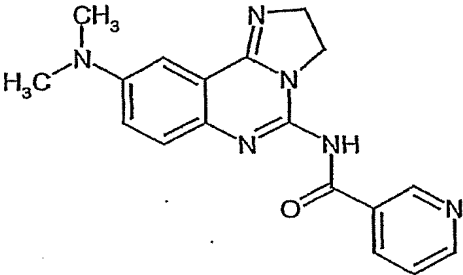
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-329		270,34	271	154 (dec.)	D
2-330		256,31	257	104-105	D
2-331		270,34	271	135-136	D
2-332		331,59	331	194 (dec.)	C

- 196 -

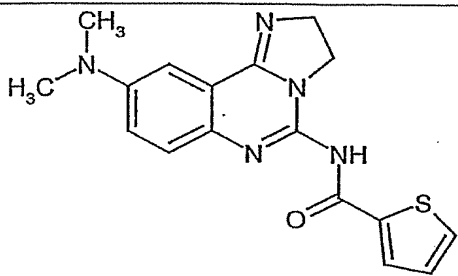
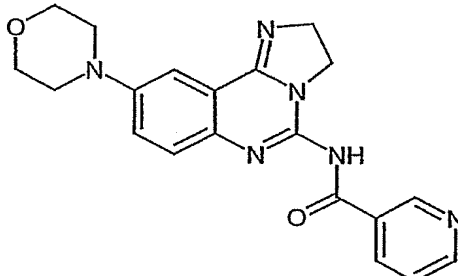
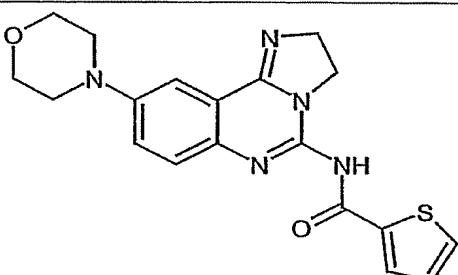
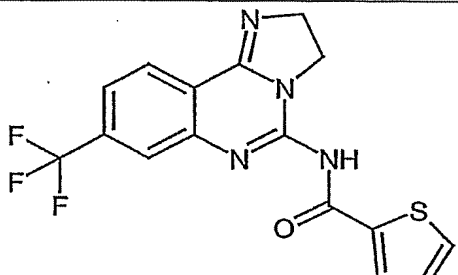
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-333		332,23	333	210-211	D
2-334		254,29	255	164 - 165	D
2-335		296,38	297	170-172	D
2-336		397,48	398	amorphous	D

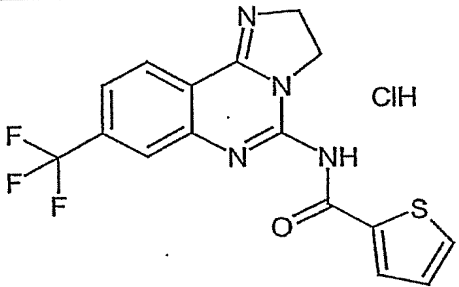
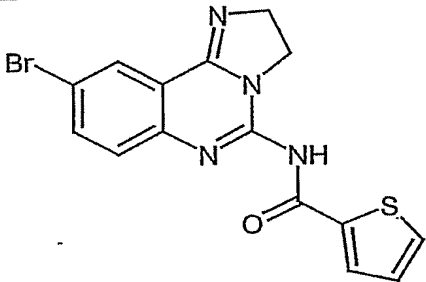
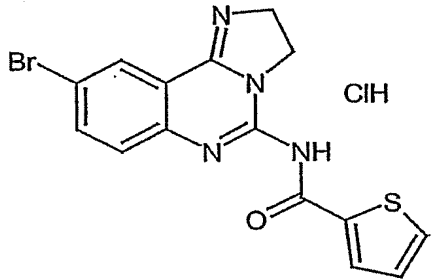
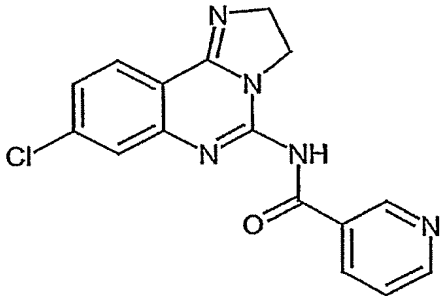
- 197 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-337		431,50	432	119 - 120	D
2-338		397,48	398	147 - 148	D
2-339		297,36	298	179 - 180	D
2-340		397,48	398	amorphous	D

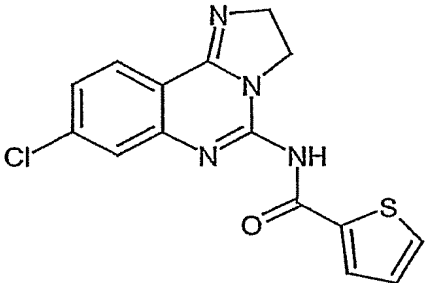
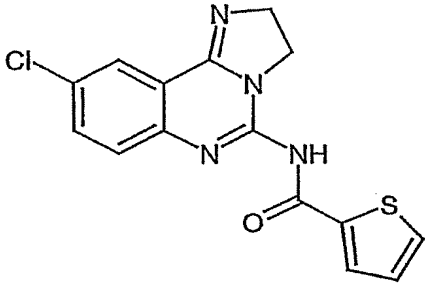
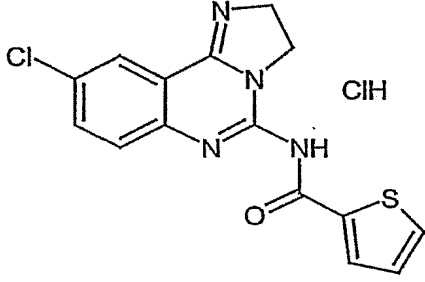
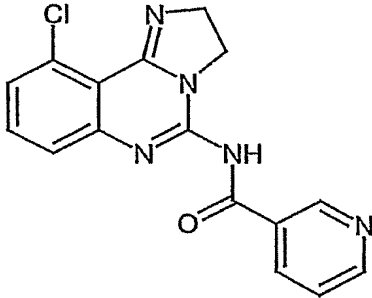
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-341		431,50	432	111 - 112	D
2-342		350,38	351	amorphous	C
2-343		288,31	289	240-241	D
2-344		302,34	303	224-225	D
2-345		334,38	335	269	C

- 199 -

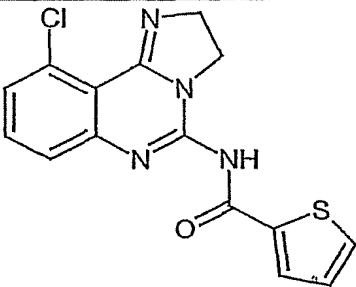
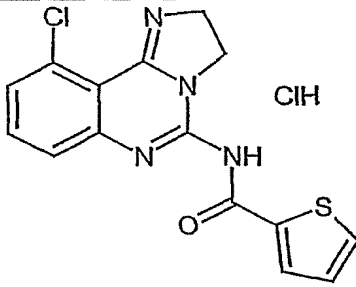
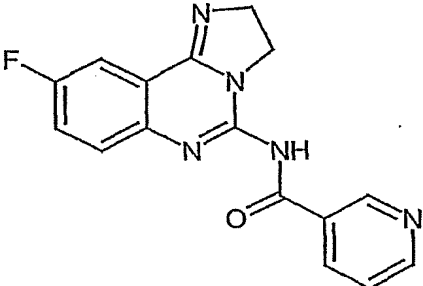
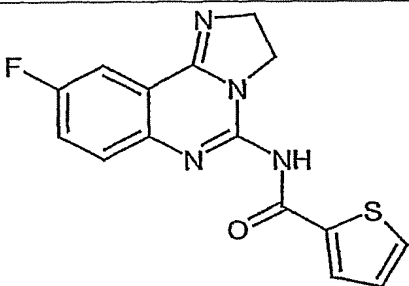
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-346		339,42	340	272	D
2-347		376,42	377	244	D
2-348		381,46	382	124	D
2-349		364,35	365	226	B

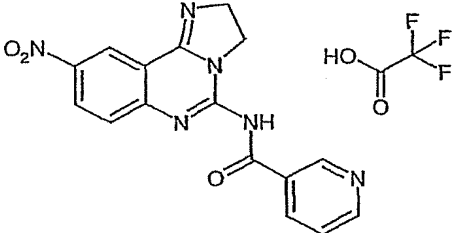
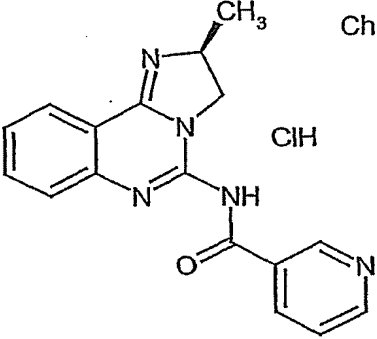
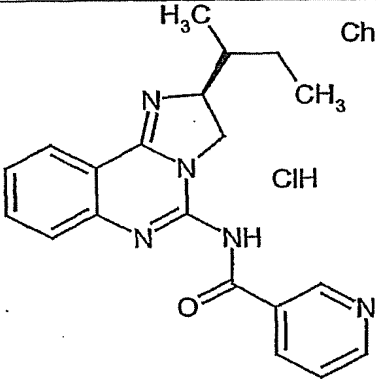
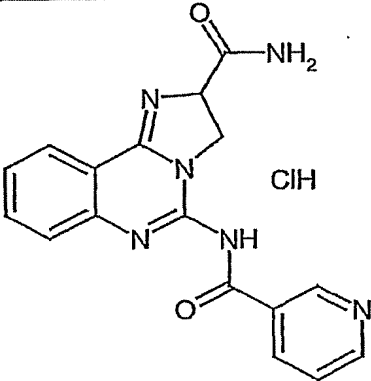
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-350	 <chem>ClC1=NC2=C(N1C(=O)Nc3ccsc3)C(=N2)C4=CC=C(C=C4)C(F)(F)F</chem>	400,81	365	292	C
2-351	 <chem>O=C(Nc1nc2cc(Br)ccc2n1)c3ccsc3</chem>	375,25	376	232	D
2-352	 <chem>ClC1=NC2=C(N1C(=O)Nc3ccsc3)C(=N2)C4=CC=C(C=C4)Br</chem>	411,71	376	275	C
2-353	 <chem>O=C(Nc1nc2cc(Cl)ccc2n1)c3ccncc3</chem>	325,76	326	254	B

- 201 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-354		330,80	331	228	C
2-355		330,80	331	174	C
2-356		367,26	331	276	B
2-357		325,76	326	243	C

- 202 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-358		330,80	331	233	D
2-359		367,26	331	227	C
2-360		309,31	310	242	C
2-361		314,34	214	315	C

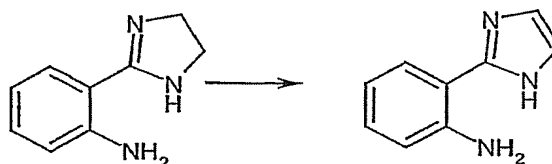
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-362		450,34	336	224	C
2-363		341,80	306	204(dec.)	D
2-364		383,88	348	230-240	D
2-365		370,80	335	274(dec.)	D

- 204 -

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-366	<p>Chiral ClH</p>	341,80	306	270(dec.)	D
2-367	<p>HCl</p>	428,88	398	273-274	A
2-368	<p>HCl</p>	403,83	368	240(dec.)	A

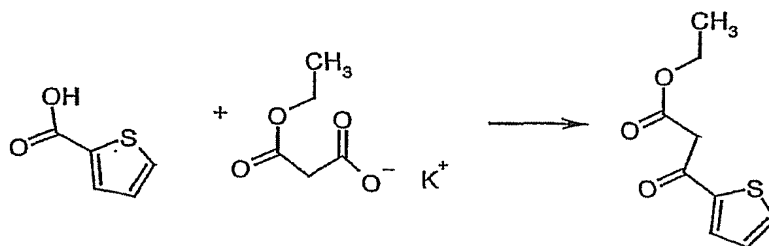
Example 3-1:**(Z)-2-Imidazo[1,2-c]quinazolin-5-yl-1-(2-thienyl)ethenol**(1) 2-(1*H*-Imidazol-2-yl)aniline

5



A mixture of 2-(4,5-dihydro-1*H*-imidazol-2-yl)aniline hydrobromide (50.0 mg, 0.207 mmol) and manganese dioxide (170 mg, 1.96 mmol) in *N,N'*-dimethylpropyleneurea (2.0 mL) was heated at 150. (bath temp.). After 1 hour, the reaction mixture was cooled to room temperature, poured into a solution of hydroxylamine hydrochloride (0.5 g) in water (50 mL), and the resulting mixture was extracted with ethyl acetate. The separated organic layer was washed with brine, dried over magnesium sulfate, filtered, concentrated under reduced pressure. The crude residue was triturated with isopropylether, and the precipitate was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by preparative thin layer chromatography (silica-gel, ethyl acetate as the eluent) to give 2-(1*H*-imidazol-2-yl)aniline (20 mg, 61% yield).

20 (2) Ethyl 3-oxo-3-(2-thienyl)propanoate

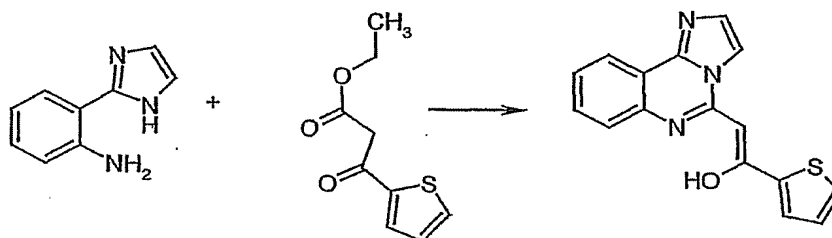


To a suspension of 2-thiophenecarboxylic acid (6.48 g, 50.57 mmol) in tetrahydrofuran (100 mL) at 5. was added 1,1'-Carbonyldiimidazole (8.61 g,

- 206 -

53.09 mmol) by portions. The mixture was allowed to warm to room temperature, and the stirring was continued for 1 hour. The reaction mixture was added into a suspension mixture of magnesium chloride (4.86 g, 51.07 mmol) and potassium 3-ethoxy-3-oxopropanoate (12.91 g, 75.85 mmol) in tetrahydrofuran (50 ml). After being stirred at 50. for 2 hours and at room temperature overnight, the reaction mixture was poured into water, and then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel (ethyl acetate/ hexane, 15/85) to give ethyl 3-oxo-3-(2-thienyl)propanoate (7.83 g, 78% yield) as a yellow oil.

(3) (Z)-2-Imidazo[1,2-c]quinazolin-5-yl-1-(2-thienyl)ethenol



A mixture of 2-(1H-imidazol-2-yl)aniline (60.0 mg, 0.38 mmol), ethyl 3-oxo-3-(2-thienyl)propanoate (74.7 mg, 0.38 mmol) and p-toluenesulfonic acid monohydrate (36.1 mg, 0.19 mmol) in toluene (30 ml) was heated at reflux for 2 hours. After cooling to room temperature, the reaction mixture was poured into aqueous saturated NaHCO_3 solution, and the resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel (ethyl acetate/ hexane, 2/3 - 1/1) to give (Z)-2-imidazo[1,2-c]quinazolin-5-yl-1-(2-thienyl)ethenol (37.0 mg, 33% yield) as a yellow powder.

Melting point: 128°C

Mass spectrometry: 294

In vitro PI3K- β inhibitory activity:

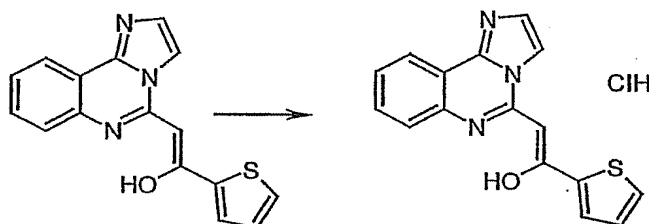
- 207 -

In vitro PI3K- γ inhibitory activity: D

$^1\text{H-NMR}$ (300 MHz, CDCl_3): d 6.11 (1H, s), 7.16 (1H, dd, $J = 3.8, 4.9$ Hz), 7.34 - 7.41 (2H, m), 7.53 - 7.60 (3H, m), 7.64 (1H, d, $J = 1.7$ Hz), 7.73 (1H, dd, $J = 1.1, 3.8$ Hz), 8.34 (1H, dd, $J = 0.9, 7.8$ Hz), 14.70 (1H, bs).

Example 3-2

(*Z*)-2-Imidazo[1,2-*c*]quinazolin-5-yl-1-(2-thienyl)ethenol hydrochloride



10

To a solution of (*Z*)-2-imidazo[1,2-*c*]quinazolin-5-yl-1-(2-thienyl)ethenol (0.06 g, 0.07 mmol) in chloroform (1.0 ml) was added a 4N solution of HCl in 1,4-dioxane (0.5 ml). The mixture was diluted with ethyl ether, and the resulting precipitate was collected by filtration, washed with ethyl ether, and dried under reduced pressure to give (*Z*)-2-imidazo[1,2-*c*]quinazolin-5-yl-1-(2-thienyl)ethenol hydrochloride (0.07 g, quantitative) as a yellow solid.

15

Melting point: 263°C (decomposition)

Mass spectrometry: 294

20

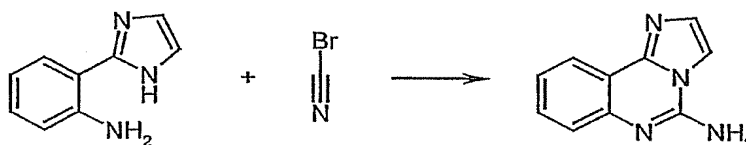
In vitro PI3K- β inhibitory activity:

In vitro PI3K- γ inhibitory activity: D

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ 6.79 (1H, s), 7.28 (1H, dd, $J = 3.8, 4.9$ Hz), 7.45 (1H, t, $J = 7.0$ Hz), 7.66 - 7.77 (2H, m), 7.82 (1H, d, 1.7), 7.91 (1H, dd, $J = 1.1, 5.0$ Hz), 8.17 (1H, dd, $J = 1.1, 3.8$ Hz), 8.30 (1H, dd, $J = 1.0, 8.0$ Hz), 8.62 (1H, d, $J = 1.7$ Hz), 14.36 (1H, br).

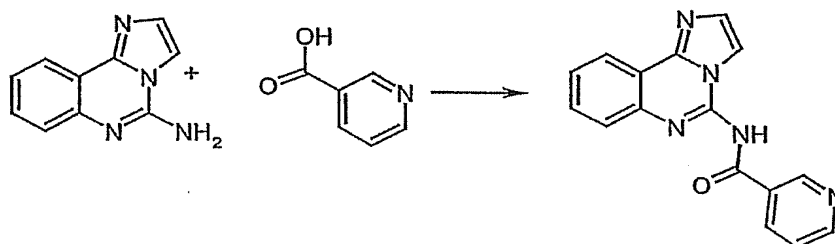
25

- 208 -

Example 4-1:*N*-Imidazo[1,2-*c*]quinazolin-5-yl nicotinamide5 (1) Imidazo[1,2-*c*]quinazolin-5-amine

10 To a solution of 2-(1*H*-imidazol-2-yl)aniline (0.06 g, 0.38 mmol) in methanol (3 ml) was added cyanogen bromide (0.05 g, 0.45 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was poured into water, and the resulting precipitate was collected by filtration, washed with acetone, and dried under reduced pressure to give imidazo[1,2-*c*]quinazolin-5-amine hydrobromide (0.06 g, 61% yield) as a white solid.

15

(2) *N*-Imidazo[1,2-*c*]quinazolin-5-yl nicotinamide

20 To a mixture of imidazo[1,2-*c*]quinazolin-5-amine hydrobromide (93 mg, 0.35 mmol) and nicotinic acid (124 mg, 1.01 mmol) and DMF (2.5 ml) at room temperature was added benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (525 mg, 1.01 mmol) followed by *N,N*-diisopropylethyl amine (0.264 ml, 1.51 mmol), and the mixture was stirred at 80 °C for 6 hours. After cooling to room

- 209 -

temperature, the reaction mixture was poured into aqueous saturated NaHCO_3 solution. The resulting precipitate was collected by filtration, washed with acetone, and dried under reduced pressure to give *N*-imidazo[1,2-*c*]quinazolin-5-yl nicotinamide (40 mg, 39% yield) as a white solid.

5

Melting point: 223-224 °C (decomposition)

Mass spectrometry: 290

In vitro PI3K- β inhibitory activity:

In vitro PI3K- γ inhibitory activity: C

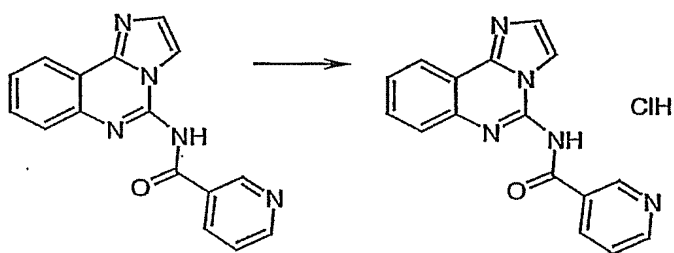
10

^1H -NMR (300 MHz, DMSO- d_6): δ 7.53 - 7.62 (3 H, m), 7.70 (1H, t, J = 7.34 Hz), 8.00 (1H, d, J = 8.10 Hz), 8.30 (1H, d, J = 7.91 Hz), 8.44 (1H, s), 8.63 (1H, d, J = 7.72 Hz), 8.81 (1H, dd, J = 1.5, 4.7 Hz), 9.49 (1H, s), 13.49 (1H, br).

15

Example 4-2

N-Imidazo[1,2-*c*]quinazolin-5-yl nicotinamide hydrochloride



20

To a solution of *N*-imidazo[1,2-*c*]quinazolin-5-yl nicotinamide (40 mg, 0.14 mmol) in methanol (20 ml) was added a 4N solution of HCl in 1,4-dioxane (0.5 ml). The mixture was concentrated under reduced pressure. The resulting solid was collected by filtration, washed with tetrahydrofuran and dried under reduced pressure to give *N*-imidazo[1,2-*c*]quinazolin-5-yl nicotinamide hydrochloride (40 mg, 89% yield) as a

25

white solid.

- 210 -

Melting point: 228 °C (decomposition)

Mass spectrometry: 290

In vitro PI3K- β inhibitory activity:

In vitro PI3K- γ inhibitory activity: C

5

^1H -NMR (300 MHz, DMSO- d_6): δ 7.60 (2H, br), 7.65 (1H, t, $J = 7.5$ Hz), 7.82 (1H, dd, $J = 7.3, 8.1$ Hz), 7.92 (1H, s), 8.02 (1H, dd, $J = 5.5, 7.9$ Hz), 8.54 (1H, d, $J = 8.3$ Hz), 8.73 (1H, s), 9.02 (1H, dd, $J = 1.3, 5.3$ Hz), 9.07 (1H, d, $J = 7.53$ Hz), 9.67 (1H, s).

10

References

- [1] Wymann MP, Sozzani S, Altruda F, Mantovani A, Hirsch E: Lipids on the move: phosphoinositide 3-kinases in leukocyte function. Immunol. Today 2000; 6: 260-264.
- [2] Stein RC, Waterfield MD: PI3-kinase inhibition: a target for drug development? Mol. Med. Today. 2000; 6: 347-357.
- [3] Sean A. Weaver, Stephen G. Ward: Phosphoinositide 3-kinases in the gut: a link between inflammation and cancer? Trends in Molecular Medicine 2001;7:455-462.
- [4] Vanhaesebroeck B, Leever SJ, Panayotou G., Waterfield MD: Phosphoinositide 3-kinases: a conserved family of signal transducers. Trends Biochem. Sci. 1997; 22: 267-272.
- [5] Fruman DA, Meyers RE, Cantley LC: Phosphoinositide kinases. Annu. Rev. Biochem. 1998; 67: 481-507.

- 211 -

- [6] Wymann MP, Pirola L: Structure and function of phosphoinositide 3-kinases. *Biochim. Biophys. Acta* 1998; 1436: 127-150.
- 5 [7] Sotsios Y, Ward SG: Phosphoinositide 3-kinase: a key biochemical signal for cell migration in response to chemokines. *Immunol. Rev.* 2000; 177: 217-235.
- [8] Toker A, Cantley LC: Signalling through the lipid products of phosphoinositide-3-OH kinase. *Nature* 1997; 387: 673-676.
- 10 [9] Stephens LR, Jackson TR, Hawkins PT: Agonist-stimulated synthesis of phosphatidylinositol(3,4,5)-trisphosphate: a new intracellular signalling system? *Biochim. Biophys. Acta.* 1993; 1179: 27-75.
- 15 [10] Stephens LR, Eguinoa A, Erdjumentbromage H, Lui M, Cooke F, Coadwell J, Smrcka AS, Thelen M, Cadwallader K, Tempst P, Hawkins PT: The G beta gamma sensitivity of a PI3K is dependent upon a tightly associated adaptor, p101. *Cell* 1997; 89: 105-114.
- 20 [11] Stoyanov B, Volinia S, Hanck T, Rubio I, Loubtchenkov M, Malek D, Stoyanova S, Van-Haesebroeck B, Dhand R, Nurnberg B, Gierschik P, Seedorf K, Hsuan JJ, Waterfield MD, Wetzker R: Cloning and characterization of a G protein-activated human phosphoinositide-3 kinase. *Science* 1995; 269: 690-693.
- 25 [12] Krugmann S, Hawkins PT, Pryer N, Braselmann S: Characterizing the interactions between the two subunits of the p101/p110gamma phosphoinositide 3-kinase and their role in the activation of this enzyme by G beta gamma subunits. *J. Biol. Chem.* 1999; 274: 17152-17158.
- 30

- 212 -

- [13] Sasaki T, Suzuki A, Sasaki J, Penninger JM: Phosphoinositide 3-kinases in immunity: lessons from knockout mice. *J. Biochem.* 2002; 131: 495-501.
- 5 [14] Sasaki T, Irie-Sasaki J, Jones RG, Oliveira-dos-Santos AJ, Stanford WL, Bolon B, Wakeham A, Itie A, Bouchard D, Kozieradzki I, Joza N, Mak TW, Ohashi PS, Suzuki A, Penninger JM: Function of PI3K γ in thymocyte development, T cell activation, and neutrophil migration. *Science* 2000; 287: 1040-1046.
- 10 [15] Li Z, Jiang H, Xie W, Zhang Z, Smrcka AV, Wu D: Roles of PLC-beta2 and -beta3 and PI3K γ in chemoattractant-mediated signal transduction. *Science* 2000; 287: 1046-1049.
- 15 [16] Hirsch E, Katanaev VL, Garlanda C, Azzolino O, Pirola L, Silengo L, Sozzani S, Mantovani A, Altruda F, Wymann MP: Central role for G protein-coupled phosphoinositide 3-kinase γ in inflammation. *Science* 2000; 287: 1049-1053.
- 20 [17] Michael A. Crackower, Gravin Y. Oudit, Ivona Kozieradzki, Renu Sarao et al: Regulation of myocardial contractility and cell size by distinct PI3K-PTEN signaling pathways. *Cell.* 2002; 110: 737-749.
- [18] Emilio Hirsch, Ornella Bosco et al: Resistance to thromboembolism in PI3K γ -deficient mice. *The FASEB Journal.* 2001; 15: 2019-2021.
- 25 [19] Ui M, Okada T, Hazeki K, Hazeki O: Wortmannin as a unique probe for an intracellular signalling protein, phosphoinositide 3-kinase. *Trends Biochem. Sci.* 1995; 20: 303-307.

- 213 -

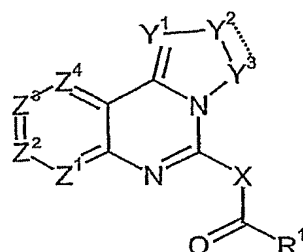
- [20] Vlahos CJ, Matter WF, Hui KY, Brown RF: A specific inhibitor of phosphatidylinositol 3-kinase, 2-(4-morpholino)-8-phenyl-4H-1-benzopyran-4-one (LY294002). J. Biol. Chem. 1994; 269: 5241-5248.

- 214 -

CLAIMS

- (1) A fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

5



wherein

X represents CR^5R^6 or NH ;

10

Y^1 represents CR^3 or N ;

Chemical bond between $\text{Y}^2=\text{Y}^3$ represents a single bond or double bond, with the proviso that when the $\text{Y}^2=\text{Y}^3$ represents a double bond,

15

Y^2 and Y^3 independently represent CR^4 or N , and

when $\text{Y}^2=\text{Y}^3$ represents a single bond, Y^2 and Y^3 independently represent CR^3R^4 or NR^4 ;

Z^1 , Z^2 , Z^3 and Z^4 independently represent CH , CR^2 or N ;

20

R^1 represents aryl optionally having 1 to 3 substituents selected from R^{11} , C_{3-8} cycloalkyl optionally having 1 to 3 substituents selected from R^{11} , C_{1-6} alkyl optionally substituted by aryl, heteroaryl, C_{1-6} alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,

25

C_{1-6} alkoxy optionally substituted by carboxy, aryl, heteroaryl, C_{1-6} alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,

or

- 215 -

a 3 to 15 membered mono- or bi-cyclic heterocyclic ring that is saturated or unsaturated, optionally having 1 to 3 substituents selected from R^{11} , and contains 1 to 3 heteroatoms selected from the group consisting of N, O and S,

5

wherein

R^{11} represents halogen, nitro, hydroxy, cyano, carboxy, amino, N-(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, N-(formyl)-N-(C₁₋₆alkyl)amino, N-(C₁₋₆alkanesulfonyl) amino, N-(carboxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, N-(C₁₋₆alkoxycarbonyl)amino, N-[N,N-di(C₁₋₆alkyl)amino methylene]amino, N-[N,N-di(C₁₋₆alkyl)amino (C₁₋₆alkyl)methylene]amino, N-[N,N-di(C₁₋₆alkyl)amino C₂₋₆alkenyl]amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl, C₃₋₈cycloalkyl, C₁₋₆ alkylthio, C₁₋₆alkanesulfonyl, sulfamoyl, C₁₋₆alkoxycarbonyl,

15

20

N-arylamino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101} , N-(aryl C₁₋₆alkyl)amino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101} , aryl C₁₋₆alkoxycarbonyl wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101} ,

25

C₁₋₆alkyl optionally substituted by mono-, di- or tri- halogen, amino, N-(C₁₋₆alkyl)amino or N,N-di(C₁₋₆alkyl)amino,

30

C₁₋₆alkoxy optionally substituted by mono-, di- or tri- halogen, N-(C₁₋₆alkyl)sulfonamide, or N-(aryl)sulfonamide,
or
a 5 to 7 membered saturated or unsaturated ring having 1 to 3 heteroatoms selected from the group consisting of O, S and N, and optionally having 1 to 3 substituents selected from R^{101}

- 216 -

wherein

R¹⁰¹ represents halogen, carboxy, amino, N-(C₁₋₆ alkyl)amino, N,N-di(C₁₋₆alkyl)amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl, pyridyl,

C₁₋₆ alkyl optionally substituted by cyano or mono- di- or tri-halogen,

and

C₁₋₆alkoxy optionally substituted by cyano, carboxy, amino, N-(C₁₋₆ alkyl)amino, N,N-di(C₁₋₆alkyl)amino, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alkyl)aminocarbonyl or mono-, di- or tri- halogen;

R² represents hydroxy, halogen, nitro, cyano, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, C₁₋₆ acyloxy, aminoC₁₋₆ acyloxy, C₂₋₆alkenyl, aryl,

a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by

hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, amino C₁₋₆alkyl, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, N-(C₁₋₆alkyl)carbonylamino, phenyl, phenyl C₁₋₆ alkyl, carboxy, C₁₋₆alkoxycarbonyl, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)amino, -C(O)- R²⁰

wherein

R²⁰ represents C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, or a 5-7

- 217 -

membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, phenyl, or benzyl,

C₁₋₆ alkyl optionally substituted by R²¹,

or

C₁₋₆ alkoxy optionally substituted by R²¹,

wherein

R²¹ represents cyano, mono-, di or tri- halogen, hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆ alkyl) amino, N- (halophenylC₁₋₆ alkyl) amino, amino C₂₋₆ alkylenyl, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkoxy, -C(O)- R²⁰¹, -NHC(O)- R²⁰¹, C₃₋₈cycloalkyl, isoindolino, phthalimidyl, 2-oxo-1,3-oxazolidinyl, aryl or a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N, and optionally substituted by hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxycarbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, aminoC₁₋₆alkyl, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, or benzyl,

wherein

R²⁰¹ represents hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N- (halophenylC₁₋₆ alkyl) amino, C₁₋₆alkyl, aminoC₁₋₆ alkyl, aminoC₂₋₆ alkylenyl, C₁₋₆ alkoxy, a 5 or 6

- 218 -

membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N, and optionally substituted by hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino or benzyl;

5

10

R³ represents hydrogen, halogen, aminocarbonyl, or C₁₋₆ alkyl optionally substituted by aryl C₁₋₆ alkoxy or mono-, di- or tri- halogen;

R⁴ represents hydrogen or C₁₋₆ alkyl;

R⁵ represents hydrogen or C₁₋₆ alkyl; and

15

R⁶ represents halogen, hydrogen or C₁₋₆ alkyl.

(2) The fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

20

wherein

X represents CR⁵R⁶ or NH;

25

Y¹ represents CR³ or N;

Chemical bond between Y²—Y³ represents a single bond or double bond, with the proviso that when the Y²—Y³ represents a double bond,

Y² and Y³ independently represent CR⁴ or N, and

30

when Y²—Y³ represents a single bond, Y² and Y³ independently represent CR³R⁴ or NR⁴;

- 219 -

Z^1 , Z^2 , Z^3 and Z^4 independently represent CH, CR^2 or N;

R^1 represents

5 C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen,
phenyl, methoxyphenyl, phenoxy, or thienyl,
 C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen,
phenyl, methoxyphenyl, phenoxy, or thienyl,

10 or

one of the following carbocyclic and heterocyclic rings selected from
the group consisting of cyclopropyl, cyclohexyl, piperidiny, piperaziny,
15 pyrroly, pyrazoly, furyl, thienyl, thiazoly, isothiazoly, oxazoly,
isoxazoly, imidazoly, isoimidazoly, pyrazoly, 1,2,3-thiadiazoly,
1,2,4-thiadiazoly, 1,2,5-thiadiazoly, 1,3,4-thiadiazoly, 1,2,3-oxadiazoly,
1,2,4-oxadiazoly, 1,2,5-oxadiazoly, 1,3,4-oxadiazoly, 1,2,3-triazole,
1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, phenyl, pyridyl, pyraziny,
20 pyrimidiny, pyridaziny, 1-benzothio-phenyl, benzothiazoly, benzimidazoly,
3H-imidazo[4,5-b]pyridiny, benzotriazoly, indoly, indazoly, imidazo[1,2-a]pyridiny,
quinoliny, and 1,8-naphthyridiny,

wherein

25

said carbocyclic and heterocyclic rings optionally substituted with 1 to
3 substituents selected from the group consisting of hydroxy, halogen,
nitro, cyano, carboxy, amino, $N-(C_{1-6}alkyl)amino$, $N,N-di(C_{1-6}alkyl)amino$,
 $N-(C_{1-6}acyl)amino$, $N-(C_{1-6}alkoxycarbonyl)amino$,
30 $N-(formyl)-N-(C_{1-6}alkyl)amino$, $N[N,N-di(C_{1-6}alkyl)amino\ methylene]amino$,
 $N[N,N-di(C_{1-6}alkyl)amino\ (C_{1-6}alkylene)methylene]amino$,

- 220 -

ene]amino, N-[N,N-di(C₁₋₆alkyl)amino C₂₋₆alkenyl]amino, C₁₋₆ alkyl-thio, C₁₋₆alkanesulfonyl, sulfamoyl, C₁₋₆alkoxy, C₁₋₆alkoxycarbonyl, pyrrolyl, imidazolyl, pyrazolyl, pyrrolidiny, pyridyl, phenyl C₁₋₆alkoxycarbonyl,

5

thiazolyl optionally substituted by pyridyl,
piperaziny, optionally substituted by C₁₋₆ alkyl or C₁₋₆alkoxy
and
C₁₋₆alkyl optionally substituted by mono-, di- or tri- halogen;

10

R² represents hydroxy, halogen, nitro, cyano, carboxy, amino, N-(C₁₋₆-alkyl)amino, N-(hydroxy C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxy C₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, C₂₋₆alkenyl, C₁₋₆alkoxy-carbonyl, aminocarbonyl, C₁₋₆acyloxy, aminoC₁₋₆ acyloxy, furyl,
morpholino, phenyl, piperidino, aryl,

15

pyrrolidiny, optionally substituted by C₁₋₆acylamino,
piperidino optionally substituted by hydroxy, C₁₋₆ alkyl, carboxy, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)aminocarbonyl,

20

piperaziny, optionally substituted by
C₁₋₆ alkyl,

25

C₁₋₆ alkyl optionally substituted by cyano, mono-, di- or tri- halogen, hydroxy, amino, N-(C₁₋₆alkyl)amino, N-(hydroxy C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, C₃₋₆ cycloalkyl, tetrazolyl, tetrahydro-pyranyl, morpholino, phthalimidyl, 2-oxo-1,3oxazolidiny, phenyl, -C(O)-R²⁰¹, pyrrolidiny, optionally substituted by C₁₋₆acylamino,

- 221 -

piperidino optionally substituted by hydroxy, C₁₋₆ alkyl, carboxy, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)aminocarbonyl, or piperazinyl optionally substituted by C₁₋₆ alkyl, wherein

5 R²⁰¹ represents hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(halobenzyl)amino, C₁₋₆alkyl, C₁₋₆ alkoxy, tetrazolyl, tetrahydropyranyl, morpholino,

10 pyrrolidinyl optionally substituted by C₁₋₆acylamino, piperidino optionally substituted by

hydroxy, C₁₋₆ alkyl, carboxy, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)aminocarbonyl,

15 or

20 piperazinyl optionally substituted by C₁₋₆ alkyl, C₁₋₆ alkoxy optionally substituted by cyano, mono-, di- or tri- halogen, hydroxy, C₁₋₆alkoxy, hydroxy C₁₋₆ alkoxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, pyrrolyl, tetrazolyl, tetrahydropyranyl, morpholino, phthalimidyl, 2-oxo-1,3oxazolidinyl, phenyl, -C(O)- R²⁰¹,

25 pyrrolidinyl optionally substituted by C₁₋₆acylamino, piperidino optionally substituted by hydroxy, C₁₋₆ alkyl, carboxy, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)aminocarbonyl,

or

30 piperazinyl optionally substituted by C₁₋₆ alkyl,

wherein

- 222 -

5 R^{201} represents hydroxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(halobenzyl)amino, C₁₋₆ alkyl, C₁₋₆ alkoxy, amino C₂₋₆ alkylenyl, tetrazolyl, tetrahydropyranyl, morpholino, pyrrolidinyl optionally substituted by C₁₋₆acylamino, piperidino optionally substituted by hydroxy, C₁₋₆ alkyl, carboxy, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)aminocarbonyl,

10

or

piperazinyl optionally substituted by C₁₋₆alkyl;

15

R^3 represents hydrogen, halogen, C₁₋₆ alkyl optionally substituted by aminocarbonyl, arylC₁₋₆ alkoxy, or mono-, di- or tri-halogen;

R^4 represents hydrogen or C₁₋₆ alkyl;

R^5 represents hydrogen or C₁₋₆ alkyl; and

20

R^6 represents hydrogen, halogen or C₁₋₆ alkyl.

(3) The fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, wherein

25

X represents CR⁵R⁶ or NH;

Y¹ represents N;

Y² and Y³ represent CR³R⁴;

30

Chemical bond between Y²—Y³ represents a single bond.

- 223 -

Z^4 represents CH;

Z^1 , Z^2 and Z^3 independently represent CH, CR^2 or N;

5

R^1 represents

C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen, phenyl, methoxyphenyl, phenoxy, or thienyl,

10

C_{1-6} alkoxy optionally substituted by phenyl phenoxy, thienyl or mono-, di- or tri- halogen,

or

15

one of the following carbocyclic and heterocyclic rings selected from the group consisting of cyclopropyl, cyclopentyl, cyclohexyl, piperidiny, piperaziny, pyrroly, pyrazoly, furyl, thienyl, thiazoly, isothiazoly, oxazoly, isoxazoly, imidazoly, isoimidazoly, pyrazoly, 1,2,3-thiadiazoly, 1,2,4-thiadiazoly, 1,2,5-thiadiazoly, 1,3,4-thiadiazoly, 1,2,3-oxadiazoly, 1,2,4-oxadiazoly, 1,2,5-oxadiazoly, 1,3,4-oxadiazoly, 1,2,3-triazoly, 1,2,4-triazoly, 1,2,5-triazoly, 1,3,4-triazoly, phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1-benzothiophenyl, benzothiazoly, benzimidazoly, 3H-imidazo[4,5-b]pyridinyl, benzotriazoly, indolyl, indazoly, imidazo[1,2-a]pyridinyl, quinolinyl, and 1,8-naphthyridinyl,

20

wherein

25

said carbocyclic and heterocyclic rings optionally substituted with 1 to 3 substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, carboxy, amino, N-(C_{1-6} alkyl)amino, N-(hydroxy C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(C_{1-6} acyl)amino, N-(C_{1-6} alkoxycarbonyl)amino, N-(formyl)-N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl) amino (C_{2-6} alkenyl) amino, N-(C_{1-6} alkane)sulfonyl amino,

30

- 224 -

- N[N,N-di(C₁₋₆alkyl)amino methylene]amino, C₁₋₆ alkylthio,
 C₁₋₆alkanesulfonyl, sulfamoyl, C₁₋₆alkoxy, C₁₋₆alkoxycarbonyl,
 pyrrolyl, imidazolyl, pyrazolyl, pyrrolidinyl, pyridyl, phenyl
 C₁₋₆alkoxycarbonyl,
 5 thiazolyl optionally substituted by pyridyl, piperazinyl optionally
 substituted by C₁₋₆ alkyl or C₁₋₆alkoxy and C₁₋₆alkyl optionally
 substituted by mono-, di- or tri- halogen;
- 10 R² represents halogen, hydroxy, nitro, cyano, amino, N-(C₁₋₆alkyl)amino,
 N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino,
 (C₂₋₆)alkenyl, C₁₋₆alkoxycarbonyl, aminocarbonyl, furyl, piperidino,
 morpholino, phenyl, pyrrolidinyl optionally substituted by N-(C₁₋₆
 acyl)amino, or N-(C₁₋₆alkyl)carbonylamino, piperidino optionally
 substituted by hydroxy, piperazinyl optionally substituted by C₁₋₆
 15 alkyl, phenylC₁₋₆alkyl, C₁₋₆alkoxycarbonyl, or aminocarbonyl;
- C₁₋₆ alkyl optionally substituted by amino, cyano, C₁₋₆alkoxycarbonyl,
 morpholino, or mono-, di- or tri- halogen,
 or
 20 C₁₋₆ alkoxy optionally substituted by hydroxy, cyano, carboxy, C₁₋₆
 alkoxy, C₁₋₆ acyl, C₁₋₆alkoxycarbonyl, amino, N-(C₁₋₆-
 alkyl)amino, N-(C₁₋₆alkyl)aminocarbonyl, N,N-di(C₁₋₆alk-
 yl)amino, N,N-di(C₁₋₆alkyl)aminocarbonyl, aminocarbonyl,
 aminoC₁₋₆ alkylcarbonyl, N-(halobenzyl)aminocarbonyl,
 25 hydroxy C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, morpholino,
 morpholinocarbonyl, pyrrolidinyl, pyrrolyl, piperidino, phthal-
 imidyl,
 or
 30 piperazinyl optionally substituted by benzyl;

- 225 -

R³ represents hydrogen;

R⁴ represents hydrogen;

5

R⁵ represents hydrogen; and

R⁶ represents hydrogen.

10 (4) The fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

X represents CR⁵R⁶ or NH;

15

Y¹ represents N;

Y² and Y³ represent CR³R⁴;

20

Chemical bond between Y²=Y³ represents a single bond

Z⁴ represents CH;

Z¹, Z² and Z³ independently represent N, CH or CR²;

25

R¹ represents cyclopropyl, cyclopentyl, cyclohexyl, 2-furyl, 3-furyl, imidazolyl, pyrimidinyl, pyridazinyl, piperazinyl, 1,2,3-thiadiazolyl, 1,3-benzothiazolyl, quinolyl, 3H-imidazo[4,5-b]pyridinyl, 1H-pyrrol-2-yl optionally substituted by C₁₋₆alkyl, 1H-pyrrol-3-yl optionally substituted by C₁₋₆alkyl, pyrazolyl optionally substituted by 1 or 2 C₁₋₆alkyl,

30

- 226 -

- isoxazolyl optionally substituted by 1 or 2 C₁₋₆alkyl,
2-thienyl optionally substituted by chloro, nitro, cyano, or C₁₋₆ alkyl,
3-thienyl optionally substituted by chloro, nitro, cyano, or C₁₋₆ alkyl,
piperidinyll optionally substituted by C₁₋₆alkoxycarbonyl, or benzyl-
oxycarbonyl, phenyl optionally substituted by 1 to 3 substituents
5 selected from the group consisting of fluoro, chloro, hydroxy, nitro,
cyano, carboxy, C₁₋₆ alkyl, C₁₋₆alkoxy, C₁₋₆alkoxycarbonyl, amino, N-
(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, N-(C₁₋₆alkoxycarbonyl)amino,
N,N-di(C₁₋₆alkyl)amino, N-(formyl)-N-C₁₋₆alkyl amino, C₁₋₆ alkylthio,
10 C₁₋₆alkanesulfonyl, sulfamoyl, pyrrolyl, imidazolyl, pyrazolyl, and
piperazinyl optionally substituted by C₁₋₆alkyl,
- pyridyl optionally substituted by 1 or 2 substituents selected from the
group consisting of chloro, hydroxy, carboxy, C₁₋₆alkoxy, C₁₋₆
15 alkylthio, amino, N-(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino,
N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, N-(C₁₋₆alkane)sulfonyl
amino, N[N,N-di(C₁₋₆alkyl)amino methylene]amino, and C₁₋₆alkyl
optionally substituted by tri halogen,
- 20 pyrazinyl optionally substituted by C₁₋₆alkyl, 1,3-thiazolyl optionally
substituted by 1 or 2 substituents selected from the group consisting of
C₁₋₆alkyl, pyridyl and N-(C₁₋₆alkoxycarbonyl)amino,
indolyl optionally substituted by C₁₋₆alkyl,
- 25 benzimidazolyl optionally substituted by C₁₋₆alkyl or tri-halo
C₁₋₆alkyl,
- 1,2,3-benzotriazolyl optionally substituted by C₁₋₆alkyl,
- 30 1,8-naphthyridinyl optionally substituted by C₁₋₆alkyl optionally
substituted by tri halogen,

- 227 -

C₁₋₆ alkyl optionally substituted by tri- halogen, phenyl, phenoxy, or thienyl,

5

or

C₁₋₆alkoxy optionally substituted by phenyl, phenoxy, or thienyl;

10 R² represents fluoro, chloro, bromo, hydroxy, nitro, vinyl, cyano, amino, aminoacetoxy, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, 2-furyl, piperidino, morpholino, phenyl, pyrrolidinyl optionally substituted by acetamido, piperidino optionally substituted by hydroxy, piperazinyl optionally substituted by methyl, benzyl, C₁₋₆alkoxycarbonyl, or aminocarbonyl,

15

C₁₋₆ alkyl optionally substituted by cyano, tri-fluoro, carboxy, methoxycarbonyl, aminocarbonyl, tert-butoxycarbonyl, tetrahydropyranyl, or morpholino,

20

C₁₋₆ alkoxy optionally substituted by hydroxy, cyano, methoxy, methoxycarbonyl, tert-butoxycarbonyl, carboxy, aminoacetyl, dimethylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, isopropylaminocarbonyl, fluorobenzylaminocarbonyl, cyclopropyl, pyrrolidinyl, piperidino, tetrahydropyranyl, morpholino, morpholinocarbonyl, 2-oxo-1,3-oxazolidin-4-yl, phthalimid-N-yl, or hydroxy C₁₋₆ alkyleneoxy,

25

R³ represents hydrogen;

30

R⁴ represents hydrogen;

- 228 -

R^5 represents hydrogen; and

R^6 represents hydrogen.

- 5 (5) The fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

10 X represents CR^5R^6 or NH;

Y^1 represents N;

Y^2 and Y^3 represent CR^3R^4 ;

15

Chemical bond between $Y^2=Y^3$ represents a single bond

Z^3 and Z^4 represent CH;

20 Z^1 and Z^2 independently represent CH or CR^2 ;

R^1 represents cyclopropyl, cyclopentyl, cyclohexyl, 2-furyl, 3-furyl, imidazolyl, 1H-pyrrol-2-yl, 1H-pyrrol-3-yl, pyrimidinyl, pyridazinyl, piperazinyl, 1,2,3-thiadiazolyl, 1,3-benzothiazolyl, quinolyl, 3H-imidazo[4,5-b]pyridinyl,

25

pyrrolyl optionally substituted by C_{1-6} alkyl, pyrazolyl optionally substituted by 1 or 2 C_{1-6} alkyl, isoxazolyl optionally substituted by 1 or 2 C_{1-6} alkyl,

30

2-thienyl optionally substituted by chloro, nitro, cyano, or C_{1-6} alkyl, 3-thienyl optionally substituted by chloro, nitro, cyano, or C_{1-6} alkyl,

- 229 -

piperidinyl optionally substituted by C₁₋₆alkoxycarbonyl, or benzyl-oxycarbonyl,

5 phenyl optionally substituted by 1 to 3 substituents selected from the group consisting of fluoro, chloro, hydroxy, nitro, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxycarbonyl, amino, N-(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, N-(C₁₋₆alkoxycarbonyl)amino, N,N-di(C₁₋₆alkyl)-amino, N-(formyl)-N-C₁₋₆alkyl amino, C₁₋₆ alkylthio, C₁₋₆alkane-sulfonyl, sulfamoyl, pyrrolyl, imidazolyl, pyrazolyl, and piperazinyl
10 optionally substituted by C₁₋₆alkyl,

pyridyl optionally substituted by 1 or 2 substituents selected from the group consisting of chloro, hydroxy, carboxy, C₁₋₆alkoxy, C₁₋₆alkylthio, amino, N-(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆acyl)amino, N-(C₁₋₆alkane)sulfonyl amino, N[N,N-di(C₁₋₆alkyl)amino methylene]amino, and C₁₋₆alkyl optionally
15 substituted by tri halogen,

20 pyrazinyl optionally substituted by C₁₋₆alkyl, 1,3-thiazolyl optionally substituted by

1 or 2 substituents selected from the group consisting of C₁₋₆alkyl, pyridyl and N-(C₁₋₆alkoxycarbonyl)amino, indolyl optionally substituted by C₁₋₆alkyl, benzimidazolyl optionally substituted by
25 C₁₋₆alkyl or tri-halo C₁₋₆alkyl,

1,2,3-benzotriazolyl optionally substituted by C₁₋₆alkyl, 1,8-naphthyridinyl optionally substituted by C₁₋₆alkyl optionally substituted by
30 tri halogen,

- 230 -

C₁₋₆ alkyl optionally substituted by tri- halogen, phenyl, phenoxy, or thienyl,

or

5 C₁₋₆alkoxy substituted by phenyl, phenoxy, or thienyl;

R² represents fluoro, chloro, bromo, hydroxy, nitro, vinyl, cyano, amino, aminoacetoxy, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, 2-furyl, piperidino, morpholino, phenyl,

10

pyrrolidinyl optionally substituted by acetamido,

piperidino optionally substituted by hydroxy, piperazinyl optionally substituted by methyl, benzyl, C₁₋₆alkoxycarbonyl, or aminocarbonyl,

15

C₁₋₆ alkyl optionally substituted by cyano tri-fluoro, carboxy, methoxycarbonyl, aminocarbonyl, tert-butoxycarbonyl, tetrahydropyranyl, or morpholino,

20

or

C₁₋₆ alkoxy optionally substituted by hydroxy, cyano, methoxy, methoxycarbonyl, tert-butoxycarbonyl, carboxy, aminoacetyl, dimethylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, isopropylaminocarbonyl, fluorobenzylaminocarbonyl, cyclopropyl, pyrrolidinyl, piperidino, tetrahydropyranyl, morpholino, morpholinocarbonyl, 2-oxo-1,3-oxazolidin-4-yl, phthalimid-N-yl, or hydroxy C₁₋₆ alkyleneoxy;

25

30

- 231 -

R^3 represents hydrogen;

R^4 represents hydrogen;

5 R^5 represents hydrogen; and

R^6 represents hydrogen.

10 (6) The fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

X represents CR^5R^6 or NH;

15 Y^1 represents N;

Y^2 and Y^3 represent CR^3R^4 ;

Chemical bond between $Y^2=Y^3$ represents a single bond

20 Z^1 and Z^4 represent CH;

Z^2 and Z^3 independently represent CH or CR^2 ;

25 R^1 represents cyclopropyl, cyclopentyl, cyclohexyl, 2-furyl, 3-furyl, imidazolyl, 1H-pyrrol-2-yl, 1H-pyrrol-3-yl, pyrimidinyl, piperazinyl, pyridazinyl, 1,2,3-thiadiazolyl, 1,3-benzothiazolyl, quinolyl, 3H-imidazo[4,5-b]pyridinyl,

pyrrolyl optionally substituted by C_{1-6} alkyl,

30

pyrazolyl optionally substituted by 1 or 2 C_{1-6} alkyl,

- 232 -

isoxazolyl optionally substituted by 1 or 2 C₁₋₆alkyl,

2-thienyl optionally substituted by chloro, nitro, cyano, or C₁₋₆ alkyl,

5

3-thienyl optionally substituted by chloro, nitro, cyano, or C₁₋₆ alkyl,

piperidiny1 optionally substituted by C₁₋₆alkoxycarbonyl, or benzyl-
oxycarbonyl,

10

phenyl optionally substituted by 1 to 3 substituents selected from the
group consisting of fluoro, chloro, hydroxy, nitro, cyano, carboxy, C₁₋₆
alkyl, C₁₋₆alkoxy, C₁₋₆alkoxycarbonyl, amino, N-(C₁₋₆alkyl)amino, N-
(C₁₋₆acyl)amino, N-(C₁₋₆alkoxycarbonyl)amino, N,N-di(C₁₋₆alkyl)-
amino, N-(formyl)-N-C₁₋₆alkyl amino, C₁₋₆ alkylthio, C₁₋₆alkane-
sulfonyl, sulfamoyl, pyrrolyl, imidazolyl, pyrazolyl, and piperazinyl
optionally substituted by C₁₋₆alkyl,

15

pyridyl optionally substituted by 1 or 2 substituents selected from the
group consisting of chloro, hydroxy, carboxy, C₁₋₆alkoxy, C₁₋₆alkylthio,
amino, N-(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino,
N-(C₁₋₆acyl)amino, N-(C₁₋₆alkane)sulfonyl amino, N[N,N-di(C₁₋₆alkyl)amino
methylene]amino, C₁₋₆-alkoxyphenylC₁₋₆alkoxy, and C₁₋₆alkyl optionally substituted by tri
halogen,

20

25

pyrazinyl optionally substituted by C₁₋₆alkyl,

1,3-thiazolyl optionally substituted by 1 or 2 substituents selected
from the group consisting of C₁₋₆alkyl, pyridyl and N-(C₁₋₆-
alkoxycarbonyl)amino, indolyl optionally substituted by C₁₋₆alkyl,

30

- 233 -

- benzimidazolyl optionally substituted by C₁₋₆alkyl or tri-halo C₁₋₆alkyl,
- 5 1,2,3-benzotriazolyl optionally substituted by C₁₋₆alkyl, 1,8-naphthyridinyl optionally substituted by C₁₋₆alkyl optionally substituted by tri halogen,
- 10 C₁₋₆ alkyl optionally substituted by tri- halogen, phenyl, phenoxy, or thienyl,
- or
- C₁₋₆alkoxy substituted by phenyl, phenoxy, or thienyl;
- 15 R² represents fluoro, chloro, bromo, hydroxy, nitro, vinyl, cyano, amino, aminoacetoxyl, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(hydroxyC₁₋₆alkyl)-N-(C₁₋₆alkyl)amino, 2-furyl, piperidino, morpholino, phenyl,
- 20 pyrrolidinyl optionally substituted by acetamido, piperidino optionally substituted by hydroxy, piperazinyl optionally substituted by methyl, benzyl, C₁₋₆alkoxycarbonyl, or aminocarbonyl,
- 25 C₁₋₆ alkyl optionally substituted by cyano, tri-fluoro, carboxy, methoxycarbonyl, aminocarbonyl, tert-butoxycarbonyl, tetrahydropyranyl, or morpholino,
- or
- 30 C₁₋₆ alkoxy optionally substituted by hydroxy, cyano, methoxy, methoxycarbonyl, tert-butoxycarbonyl, carboxy, aminoacetyl, dimethylamino, aminocarbonyl, methylaminocarbonyl, di-

- 234 -

methylaminocarbonyl, isopropylaminocarbonyl, fluorobenzyl-
aminocarbonyl, cyclopropyl, pyrrolidinyl, piperidino, tetra-
hydropyranyl, morpholino, morpholinocarbonyl, tetrazolyl, 2-
oxo-1,3-oxazolidin-4yl, phthalimid-N-yl, or hydroxy C₁₋₆
alkyleneoxy;

R³ represents hydrogen;

R⁴ represents hydrogen;

R⁵ represents hydrogen; and

R⁶ represents hydrogen.

(7) The fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

X represents CR⁵R⁶ or NH;

Y¹ represents N;

Y² and Y³ represent CR³R⁴;

Chemical bond between Y²=Y³ represents a single bond

Z³ and Z⁴ represent CH;

Z¹ and Z² independently represent CH or CR²;

R¹ represents 3H-imidazo[4,5-b]pyridinyl, benzimidazolyl

- 235 -

pyridyl optionally substituted by hydroxy, amino, acetamido, methoxybenzyloxy or methylsulfonylamino,

or

5 1,3-thiazolyl optionally substituted by 1 or 2 methyl;

R^2 represents fluoro, chloro, bromo, morpholino, piperazinyl, methylpiperazinyl, methyl, tri-fluoro methyl, or C_{1-6} alkoxy optionally substituted by hydroxy, cyano, carboxy, dimethylaminocarbonyl, 10 tetrahydropyranyl, morpholino, morpholinocarbonyl, tetrazolyl, or phthalimid-N-yl;

R^3 represents hydrogen;

15 R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents hydrogen.

20

(8) The fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

X represents CR^5R^6 or NH ;

25

Y^1 represents N ;

Y^2 and Y^3 represent CR^3R^4 ;

30

Chemical bond between $Y^2=Y^3$ represents a single bond;

- 236 -

Z^1 , Z^3 and Z^4 represent CH;

Z^2 represents CR^2 ;

5 R^1 represents 3H-imidazo[4,5-b]pyridinyl, benzimidazolyl
 pyridyl optionally substituted by hydroxy, amino, acetamido,
 methoxybenzyloxy or methylsulfonylamino,

 or

10

 1,3-thiazolyl optionally substituted by 1 or 2 methyl,

15

R^2 represents fluoro, chloro, bromo, morpholino, piperazinyl, methyl-
 piperazinyl, methyl, tri-fluoro methyl, C_{1-6} alkoxy optionally sub-
 stituted by hydroxy, cyano, carboxy, dimethylaminocarbonyl, tetra-
 hydropyranyl, morpholino, morpholinocarbonyl, tetrazolyl, or
 phthalimid-N-yl;

20

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

25

R^6 represents hydrogen.

- (9) The fused azolepyrimidine derivative of the formula (I), its tautomeric or
 stereoisomeric form, or a salt thereof as claimed in claim 1, wherein said
 derivative is selected from the group consisting of the following compounds:

30

N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

- 237 -

2-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-pyridin-3-ylethylenol;

5 N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

6-(acetamido)-N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

10 N-{5-[2-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide;

15 2-({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)-N,N-dimethylacetamide;

2-[7-methoxy-8-(tetrahydro-2H-pyran-2-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;

20 2-[8-(2-hydroxyethoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;

25 ({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)acetic acid;

4-({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)butanoic acid;

30 ({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)acetonitrile;

- 238 -

- 2-[7-methoxy-8-(2H-tetrazol-5-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;
- 5 2-[7-methoxy-8-(4-morpholin-4-yl-4-oxobutoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;
- 5-[1-hydroxy-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)vinyl]pyridin-3-ol ;
- 10 N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;
- 6-(acetamido)-N-(7,9-dimethoxy-8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 15 N-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;
- 5-hydroxy-N-(7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 20 N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-[(4-methoxybenzyl)oxy]nicotinamide;
- N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-
- 25 hydroxynicotinamide;
- 5-hydroxy-N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 30 N-{8-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

- 239 -

N-(7-bromo-8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

5 6-amino-N-(8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

10 1-(1H-benzimidazol-5-yl)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)ethylenol;

2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2,4-dimethyl-1,3-thiazol-5-yl)ethylenol;

15 N-(9-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

N-(8-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

20 N-(8-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

N-(8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

25 N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

30 N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1H-benzimidazole-5-carboxamide;

- 240 -

- N-(7-fluoro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
- 5 N-(7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
- 10 6-(acetamido)-N-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 1-(1H-benzimidazol-5-yl)-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)ethylenol;
- 15 N-{5-[1-hydroxy-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)vinyl]pyridin-2-yl}acetamide;
- 6-methyl-N-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 20 1-(1H-benzimidazol-5-yl)-2-[8-(4-methylpiperazin-1-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]ethylenol;
- N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 25 N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 30 N-[7-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1H-benzimidazole-5-carboxamide;

- 241 -

N-(7,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

5 N-{5-[2-(7,9-dimethoxy-8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide;

N-{5-[2-(7-bromo-9-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide; and

10

2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-pyridin-3-ylethanol;

15 (10) A medicament comprising the fused azolepyrimidine derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

(11) The medicament as claimed in claim 10, further comprising one or more pharmaceutically acceptable excipients.

20

(12) The medicament as claimed in claim 10, wherein the fused azolepyrimidine derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is a PI3K inhibitor.

25 (13) The medicament as claimed in claim 10, wherein the fused azolepyrimidine derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is a PI3K- γ inhibitor.

30 (14) The medicament as claimed in claim 10 for prophylaxis and/or treatment of inflammatory or immunoregulatory disorder.

- 242 -

- (15) The medicament as claimed in claim 14 for prophylaxis and/or treatment of asthma, rhinitis, allergic diseases, autoimmune pathologies, rheumatoid arthritis, Grave's disease, and atherosclerosis.
- 5 (16) The medicament as claimed in claim 10 for prophylaxis and/or treatment of neurodegenerative disorders, Alzheimer's disease, or focal ischemia.
- (17) The medicament as claimed in claim 10 for prophylaxis and/or treatment of diabetes, cancer, myocardial contractility disorders, heart failure, ischemia,
10 pulmonary hypertension, renal failure, or cardiac hypertrophy.
- (18) Use of the fused azolepyrimidine derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 for manufacturing a medicament for the treatment and/or prevention of an
15 inflammatory disorder or disease.
- (19) Use of the fused azolepyrimidine derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 for manufacturing a medicament for the treatment and/or prevention of asthma,
20 rhinitis, allergic diseases, or autoimmune pathologies.
- (20) Use of the fused azolepyrimidine derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 for manufacturing a medicament for the treatment and/or prevention of diabetes,
25 cancer, myocardial contractility disorders, heart failure, ischemia, pulmonary hypertension, renal failure, and cardiac hypertrophy.
- (21) Use of the fused azolepyrimidine derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 for
30 manufacturing a medicament for the treatment and/or prevention of disorder or disease associated with PI3K activity.

- 243 -

- 5 (22) Use of the fused azolepyrimidine derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 for manufacturing a medicament for the treatment and/or prevention of disorder or disease associated with PI3K- γ activity.
- 10 (23) Process for controlling an inflammatory disorder or disease in humans and animals by administration of a PI3K inhibitory effective amount of a compound according to claim1.
- (24) Process for controlling an inflammatory disorder or disease in humans and animals by administration of a PI3K- γ inhibitory effective amount of a compound according to claim1.
- 15 (25) Process for controlling an asthma, rhinitis, allergic diseases, or autoimmune pathologies, in humans and animals by administration of a PI3K- γ inhibitory effective amount of a compound according to claim1.
- 20 (26) Process for controlling a diabetes, cancer, myocardial contractility disorders, heart failure, ischemia, pulmonary hypertension, renal failure, and cardiac hypertrophy, in humans and animals by administration of a PI3K- γ inhibitory effective amount of a compound according to claim1.

INTERNATIONAL SEARCH REPORT

PCT/EP 03/10377

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 C07D487/06 C07D519/00 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

PAJ, WPI Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 644 354 A (HARDTMANN GOETZ E ET AL) 22 February 1972 (1972-02-22) cited in the application column 1, line 37 -column 1, line 49; claims; examples 1-5 ---	1-9
A	UI M ET AL: "Wortmannin as a unique probe for an intracellular signalling protein, phosphoinositide 3-kinase" TIBS TRENDS IN BIOCHEMICAL SCIENCES, ELSEVIER PUBLICATION, CAMBRIDGE, EN, vol. 20, no. 8, August 1995 (1995-08), pages 303-307, XP004222293 ISSN: 0968-0004 cited in the application the whole document --- -/--	1-26



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

19 January 2004

Date of mailing of the international search report

30/01/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Schmid, A

INTERNATIONAL SEARCH REPORT

PCT/EP 03/10377

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>VLAHOS C J ET AL: "A SPECIFIC INHIBITOR OF PHOSPHATIDYLINOSITOL 3-KINASE, 2-(4-MORPHOLINYL)-8-PHENYL-4H-1-BENZOPYRAN-4-ONE (LY294002)" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 269, no. 7, 18 February 1994 (1994-02-18), pages 5241-5248, XP002023636 ISSN: 0021-9258 cited in the application table 1 the whole document</p>	1-26

INTERNATIONAL SEARCH REPORT

PCT/EP 03/10377

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 23-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1,2 (partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2 (partly)

Present claims 1,2 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/products/apparatus/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to present claim 3 which appear to be supported by the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

PCT/EP 03/10377

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 3644354	A	22-02-1972	BE 738885 A	16-03-1970
			DE 1946188 A1	16-04-1970
			FR 2018180 A1	29-05-1970
